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Sexual Assault: The Victim's Psychology and Related Problems

OLGA KNOPF, M.D.

I

During the past 10 or 15 years the sexual assault on women, adolescents, and children has aroused the concern of the medical and allied sciences. Some members in affected departments of The Mount Sinai Hospital and School of Medicine, including the Emergency Room, joined forces to assist victims in regaining their physical and mental health. The detrimental consequences of limiting attention to physical first aid already were recognized by medicine, especially the psychiatric branch.

We at Mount Sinai envisioned a project that would include research not only into the personality of the victim and her assailant but also into the circumstances that have led to this "new epidemic."

The first phase, first aid to the victim and prevention of eventual physical consequences has been accomplished. Thanks is to be given to the unstinting and entirely voluntary efforts of the planners.

The second phase is in the process of being developed. There are quite a number of questions that need answering and some that need more investigation from allied sciences. Finally, means must be developed to educate the public and to find methods of prevention of this occurrence.

The following are reflections, assumptions and conclusions by the author, a member of the psychiatric staff. The ideas expressed are the result of a long lifetime of experiences, of changing mores, especially of witnessing the upheaval that for the past few years has been confusing the relationship between the sexes. Most of what I present here may have to be corroborated, and adjusted to the times which are fluctuating at a more rapid pace than ever. These comments are presented with the intention of awakening public thinking to bring more order into the chaos of human relationships.

Until a few years ago rape was considered a dirty word and was neither mentioned in polite society nor attended to by the student of human nature. Child or adolescent molestation was just as much hushed up lest it reflect poorly on the reputation not only of the child but the entire family. There were only a few scientists who paid attention to these occurrences and realized the consequences for the future emotional development of the child unless the trauma was properly handled by the parents, especially the mother. Doctor

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Karl Abraham was one of the courageous people who dealt with this kind of injury (1). Freud was another, but he found himself in a dilemma. In his paper *Dora* (2), he stated that he heard so often, especially from female patients, that when they were children they had been molested to various degrees, including penetration, that these stories simply could not have been true; he assumed that they were the result of the children's fantasies which they could not distinguish from reality. Freud himself was a very prim and reserved personality who could not conceive the liberties members of one family took with each other, without considering the consequences these activities may have on the child victims as they grew up. Since his patients came mostly from middle and upper middle class families, who, he believed, were better educated and therefore more self-restrained, he interpreted the stories he heard as fantasies.

In the poorer part of the population with its lack of privacy due to cramped living quarters, temptation in this direction was assumed to be more prevalent. It prepared the young ones in a more drastic way for "the facts of life" and found them more responsive to experimentation. The psychological consequences that manifested themselves in most children who for various reasons did not confide the abuse they suffered to their mothers, or were not believed when they did, have only recently been properly evaluated by Dr. Joseph Peters (3).

Since then much has been changed in the role of the woman in society and with it the relationship between men and women. The turning point seems to have begun in earnest after the First World War, yet sexual assault was still a rare occurrence and when it did happen it was hushed up in order to protect the reputation of the victim and her family.

The lack of attention, or rather apathy, continued until a few years ago when the victimization of women of all ages and all walks of life reached such dimensions that one could no longer overlook it.

In addition to Amir (4), other researchers began to collect material (5, 6) in Boston, in Philadelphia and other cities. Their reason was the fact that the number of sexual assaults had multiplied within a few years. Up to the early seventies this crime has been silenced for so long because of its sexual connotation and most women were afraid for their reputation if it became known that they had been assaulted, irrespective of the circumstances. It was finally discovered that the sexual aspect was actually a very subordinated element in the whole concept, at least for the perpetrator. Rape actually is an assault of one human being upon another human being, usually a female victim. The objective is to rob the victim of all possessions. The sexual organ is just one more weapon applied during the assault. The attacker usually has some other weapon that works to his advantage as well as the element of surprise and shock that handicaps the victim's resources for clear thinking. The sexual demands made against the will of the victim are intended further to humiliate in addition to rob.

Researchers and other well-informed people are now convinced of these facts, but the general public still thinks otherwise and regards rape as a sexual activity only. Moreover, very many are, to this day, inclined to attribute rape mostly to feminine provocation. It must be kept in mind that we have been living until recently in a male-oriented society in which women were more or less subjugated by the rules set up by men.

The legal definition of rape is "forced or attempted violent penetration of the victim's body without consent, including oral and anal sodomy." It is punishable with up to 15 years of imprisonment. Because of the difficulties of apprehending the perpetrator and securing proof that force was used, only a few of the rapists are brought to justice. Worse, because of the misconception, still widespread, that most of these crimes are provoked, only a small portion of convictions are obtained. In addition, a relatively large number of women know their assailant (30%) and are hesitant to bring charges for various reasons. The man is either related to them, a friend of the family, a date, or a business acquaintance. Some who live in the neighborhood of the attacker are simply afraid of retaliation.

With the recognition that rape is an act of violence, more and more victims became willing to discuss their ordeal with trained counselors, enabling researchers to gain better information and to help the victims regain their emotional equilibrium.

Soon after Amir published his first textbook on this subject, Ann Wolberg Burgess, professor of nursing at Boston College and Lynda Lytle Holmstrom (5), professor of Sociology at the same College, started the first rape-victim clinic in Boston and accumulated first-hand knowledge regarding this delicate subject. They divided the various forms of assault into three main groups: First *Rape Trauma* will occur when a woman is penetrated by a man without her consent. There are also other forms of violation that are included in this definition. The second category is called *Accessory to Sex* where there is inability to give consent, as with children or mentally defective women, both of whom do not understand what is happening to them. The third category is *Sex Stress.* An anxiety reaction in the victim results from a sexual situation in which both parties originally consented and where "something went wrong." For example, when the man demands sexual acts with which the woman is not prepared to comply or when the man becomes violent. There are other situations like social exposure or unexpected embarrassment.

This paper will confine itself to the first category, the psychological manifestations and consequent reactions during and after the assault. It will also offer a possible connection between the tragic increase in the occurrence of this crime and the rapid emergence of women from the home.

II

In the Coconut Grove fire in Boston in the early forties, there perished a large number of mostly young people. Dr. Erich Lindeman had the opportunity of treating a number of survivors who had lost one or more family members or friends in the disaster. These survivors showed reactions of what Dr. Lindeman called *acute grief* and they were striking in their similarity to each other. Although not all of these showed all of the manifestations, some showed them in various degrees, yet they were manifest in all of them. Common were the following complaints: sensations of somatic distress in various organ systems, tightness in the throat, choking, shortness of breath, need for sighing, and an empty feeling in the abdomen, lack of muscular power and an intense subjective distress described as tension or mental pain. There was a tendency to avoid mentioning the deceased at all cost, to refuse visits from friends; some also showed a slight sense of unreality. There was a strong preoccupation with feelings of guilt, self-accusations of negligence or exaggerated minor omissions. There was disconcerting loss of warmth in relation to other people, irritability and anger ("why me?"); these feelings of hostility disturbed the patients and they feared approaching insanity. There was restlessness and inability to sit still, moving about in an aimless fashion.

Not only were the symptoms very similar but also the circumstances that created them. While in normal grief the loss of the love object usually looms on the horizon for quite a while in the case of death coming after an illness or in old age, the survivor is to a certain degree prepared for the loss even if the end comes rather suddenly and unexpectedly, for something in the survivor had anticipated it. Lindeman described acute grief in contradistinction to normal grief. He called acute grief *a syndrome with psychological and somatic symptomatology.* Acute grief is caused by the suddenness of the loss of the love object, the complete unpreparedness for it and almost the opposite of the expectations of the actual happening. As in the fire, the survivors had expected the participants of the dance to have a good time, while instead their friends died miserably and painfully.

It was found that the symptoms that developed after a rape were very similar to the ones called acute grief. In rape, a woman on her way to a party, or coming home from work in anticipation of a date with her boy friend or seeing her children or hoping for a good time with her husband, suddenly finds herself exposed to a life threat, to humiliation, pain, degradation and subsequent loss of self-respect. The contrast between the expectation and the reality in either case increases the confusion and the subsequent let-down.

Women are very reluctant to go into details about their ordeal and we can only guess from their subsequent behavior what had been going on inside of them during their suffering and in the aftermath. The grief and shock made them afraid of going out unescorted or being alone at home according to the place where the trauma occurred. Some moved to other neighborhoods, moved in with friends or left town. Some returned home to their families as if they needed shelter, as when they were small children. Some changed jobs, some changed their calling and most of them developed aversion to sexual activity, as such, to men, some temporarily, some permanently. In addition to all these manifestations, some of them came out with a slight feeling of unreality, fearing the trauma has driven them to insanity; and some developed amnesia with the same fear.

Psychosomatic complaints are also often noticeable as described by Burgess and Holmstrom. A further similarity between Lindeman's acute grief and the rape trauma syndrome is the sense of guilt that develops in great many victims. Trivial items such as having used the wrong street, gone at the wrong time, or having used the wrong tactic that might have prevented the incident at all tortures them even in cases in which they were faced with a gun or a knife or a man of strong physique.

The similarity between the syndrome called acute grief and rape trauma syndrome is startling. The latter, too, behave like people in acute grief. Mourning is regarded as a normal reaction to the loss of a love object. It is expected to become milder within a few weeks and to disappear within a few months. In acute grief, the assistance of a psychiatrist or counselor is necessary and the same holds true for the rape victim. Unless the latter receives proper counseling the person who was exposed to sexual assault will show an intensified reaction to the sudden and unexpected trauma. They are in mourning. But in the case of rape, nobody has actually died—a physical death, that is. But something died within a woman who was forced against her will to submit her body to the whim of a stranger, to relinquish her integrity as a person, her privilege of self-determination and the ideals she had about herself. To make matters worse, she is forced to let her attacker take privileges that she may have reserved for the man she loves, in which case she may interpret her ordeal as a betrayal of faith.

III

In order to understand what happened, we must discuss some portion of the making of the personality. Every person has an ego-ideal. This consists of all the superlatives we would like to accomplish in our lives. The ego-ideal originates in infancy and is modeled by the idealized parent-image at a time when the child is too young to be critical and be discriminating. The ego-ideal, together with the super-ego (conscience) becomes modified through the influence of other people we admire as we go along, acquire judgment, and meet the realities of life. Yet within ourselves, even if acknowledged as fantasy, there remains the vestige of an image of unsurpassed beauty, strength, intellect, bravery, morality and whatever the cherished values of the individual are.

Included in this image is also a picture how we would behave in times of stress; whether we would be strong and faithful to our principles, even at the point of facing pain, humiliation and, perhaps death. The number of people who preferred death to being untrue to their cause has been amply proven in the course of history. These thoughts about oneself and the image about one's own moral fortitude are not shared with anyone, no matter how intimate and close we may be with another person. In the case of rape, the victim must make a choice between living up to her ideals or betraying them by giving in. The suddenness of the attack has frightened and perplexed her, making clear thinking even more difficult. The danger to her life is very real and the desire to preserve life is by far stronger than she anticipated. The decision to surrender her principles and remain alive will leave her with a feeling of guilt afterwards. The number of women who did put up a fight and were severely injured or even lost their lives has never been statistically ascertained, but I am sure, it is larger than one would generally assume. These guilt-feelings have long been puzzling to me since the odds in this situation are against the victim from the start. The reaction to this self-betrayal is the cause for the change of life style that so often follows this dreadful experience. It is a form of running away from a danger, or from a frightening sight, from oneself, but unfortunately the victim carried the memory of the ordeal with her.

The "self-betrayal" is not the only reason for the guilt feelings. There is another, equally powerful and painful in retrospect.

Before I describe the second source of guilt feelings, a short explanation of the physiology of sexual excitation and gratification is necessary. Sexual arousal can occur from the stimulation of almost any part of our body as well as our fantasy. Whatever kind of stimulation takes place it is accompanied by a response in the genital region, the only place in our body that can reach a sexual climax. The latter is reached by the physical union of two adults (normal intercourse), or by mechanical stimulation without a partner, but with the help of our fantasy.

On first touch, the woman will probably respond automatically with a feeling of sexual arousal accompanied by the secretion of the local glands to moisten the expected penetration. In case of rape, a few moments later, as she comes out of the initial shock and regains some of her awareness this response will disappear and turn into dryness and revulsion. The terror, too, will numb any response that can possibly occur. However, some of the rapists, especially in cases where the man, having gained access to the victim's apartment, can take his time and try various means to stimulate the victim, can excite the woman to the point of orgasm, even if her eyes are covered and her hands tied and she never learns what her tormentor looks like. If he succeeds in this endeavor, he has exposed her to the epitome of degradation and self-contempt.

A classic example of the rape crisis syndrome and its consequences can be found in the life of T. E. Lawrence, who, while he was alive was called the King of Arabia, during and after the First World War. He was suspected of having been a homosexual although no definite proof has ever been established. However, he was captured and tortured sexually during one of his campaigns. He never gave any details about this incident but in one of his letters he mentioned the "defilement at Der'a" by his political opponents in the Near East in 1922. He left the active service abruptly in the same year, returned to London and enlisted as a mechanic in the Royal Air Force. He also changed his name to Ross. This change from the exalted position he had during the war and the important role he played during the Versailles Peace Conference is indicative of the severe psychic trauma he must have sustained, although the details were kept from the general public. This self-punishment did not bring him peace and we see him enlisted as a foot soldier in the Indian Army in 1925. In 1927 he changed his name to Shaw. He explained these various moves as an escape from "too much publicity." Soon after he returned to London, spending his time writing his biography and racing cars, mostly motorcycles, at top speed through the streets of London until he died in a motorcycle accident caused by speeding in 1935.

This tragic change of life style is a typical form of escape and self-punishment found in many sexual assault victims. The anger that cannot express itself on the enemy, is turned inward and leads to depression and self-reproach.

I choose deliberately the sample of a male subjected to similar humiliation and defilement as a woman raped. The reactions were the same as the female victim develops, but I do not know of any woman as well known and admired as Lawrence, who had to suffer a similar fate. I also want to show that the rape crisis syndrome is not characteristic for women victims only, just as acute grief is not sex-bound.

These biological facts should be part of the counseling to reassure the woman that she was neither unfaithful nor a loose woman, but a victim of mechanical abuse. Unfortunately the husbands and the boyfriends of these women do not know the facts either, otherwise their attitude towards the victim would be different. It is precisely at that moment that the woman needs reassurance, trust and love from the family and friends, especially from "her man" and not "magnanimous forgiveness," since she had done nothing that was culpable.

This difference between actual sexual excitation and mechanical stimulation and its public misinterpretation is the second reason for guilt feelings the woman may suffer from after she comes out of her ordeal. The vagina has no eyes and this fact, too, should be widely used in counseling and public education.

Not all women react to these experiences in the same way or to the same degree. Personalities are developed according to the family mores, their kind of values, their cultural background, their religious beliefs and the role sexual activity plays in the life of the individual woman.

Neither the victims nor their kin talk much about their family disgrace. While the victims feel relief if they can air their feelings, look for and get sympathy and emotional support from the people around them, the latter have sometimes difficulties in keeping up the warmth and compassion they originally felt. They tire easily having to listen to the same story over and over again (the repetitive retelling is for many women an attempt to get the poison out of their system); the family is loathe to seek assistance from the law, fearing the publicity and help only half-heartedly to assist the victim to find the attacker. Fear of retaliation, fear of violence keeps many a family from accusing a neighbor although they know well that it was he who violated their daughter. And as time goes on a slight suspicion returns that the victim might not have been as innocent as she claims to be.

Here and there a woman is more articulate and tries to recall her suffering in detail, but it takes a number of years until sufficient distance from the incident has been reached to give a more objective view of what happened, to herself and the people involved.

One of these who did invaluable service to all interested in this almost national disease is Dr. Deena Metzger (6). She, too, does not say anything about the incident itself; the only inference that can be drawn as to where it happened, indoors or outdoors, was her remark: "when it was all over I found myself on the floor naked". She told us how she felt after the ordeal and how she managed to live on. She bore out the contention that husband and boy friends have almost as hard a time as the victim getting over the assault, but for different reasons. Initially they are sympathetic and try to reassure the victim of continued devotion. They share the victim's endeavors to find the culprit; but their motivation seems to be more pride and need for avenging the intrusion into and defilement of their property, than compassion for the victim. The woman, on her part, in trying to find the attacker, hopes she can regain some of her inner self by seeing the rapist in person and, if possible, bringing him to justice. The need of the injured woman for prolonged reassurance remains unfulfilled and gradually the relationship between her and her man deteriorates. In the case of Dr. M. divorce followed within one year. It is the old story that it was the victim who was responsible for the crime although the facts proved to be otherwise.

IV

There are universal misunderstandings that make it difficult for the victim to regain her former self and return to her former social associations. One of the most misleading ideas is the widespread belief that the woman really enjoys what is happening to her. For reasons described before some of them undoubtedly do. Some others, if under the influence of alcohol at the time may have distorted recollections afterwards. There is a general saying most men will use when the topic of rape comes up: "Since the woman has to take it, she may just as well enjoy it." The man who makes that quip did not pay any attention to the woman's side. In his masculine vanity it does not occur to him that a woman has her preferences, too, just like a man.

Another of the popular misconceptions is laid by the Women's Liberation Movement at the doorstep of Freud. They accuse him of attributing to all females, fantasies of being raped and, therefore, they claim nobody has any sympathy for a misused woman. It is quite correct that psychoanalysis speaks of raping fantasies in the preadolescent girl. The budding female usually has a hero like a movie star or the top football player in her high school. They dream about swooning in his arms and surrendering entirely to his whims. But if the hero would really mean business, the girl would run as far as the North Pole. All she has meant and fantasied about was to be enveloped into his arms and cuddled like a baby the same way she was cuddled by her father when she was little. This has nothing to do with adult sexuality except the common name.

These female fantasies have, in fact, their male counterpart—conveniently overlooked by the radical feminists. The adolescent boy has fantasies about his conquests of women and raping fantasies are not uncommon during the period in which a boy becomes a man. These are natural occurrences and are similar to the young person's dream of "Some day becoming President of the United States." The further the youngster of either sex progresses in his maturing, the more realistic became the daydreams of his future. The kind of man (and his background) who carries these raping fantasies into reality will have to be subjected to further studies before the ever-growing threat to women can be checked.

V

The only way to assist recovery known to us at the present time is counseling. A trained social worker or nurse makes contact with the victim in the emergency room and stands by during the medical and legal procedures. She is the only prop a victim can hold on to during the first hours after the assault. She also protects her from being questioned needlessly and acts as a chaperone during the necessary medical examination. The latter, if not tactfully conducted, can be as bad a trauma to the victim as the assault was, unless there is also another female present known to the victim and to reassure her. The counselor also stands by during the procedures necessary to prevent pregnancy and venereal disease. She also acts as an intermediary between the victim and her family—i.e., being the parents, the husband or the boy friend. All of them need reassurance themselves and instruction on how to behave towards the victim constructively. In case the woman shows signs of exaggerated excitation or has a history of previous psychiatric attention, for whatever reason, a psychiatric consultant will take over.

The decision to press charges is not an easy one for the victim. It demands conferences with the police authorities, her own lawyer, the court hearings, and the trial. Special escorts, selected from among the hospital volunteers will accompany the women on these errands and help bolster their courage. The court hearing and the trial were particularly hard for these women, because of the misunderstanding about the causes of rape. Since the knowledge that rape is an act of assault has become accepted, the judge and even the defense lawyer have changed their tune and are trying less hard to make the victim into the perpetrator. Changes in the law also make it easier to have the charge stick once they are made.

The woman may choose not to press charges for reasons of her own, but she should do so out of compassion with other women defiled and to be defiled at some later time. She could make her deposition to the police without giving her name. And it could not be used without her permission. A large number of rapists are repeaters and they usually use the same method each time. The more that is known about these methods the easier may be the apprehension of the perpetrator.

VI

There are still some unanswered questions that need clarification before this new menace can be put under control.

Problem 1. Should a woman fight off the attacker or should she submit and get the ordeal over with? If she fights back she might risk or even lose her life. Quite a few died before and some after having been attacked. If she submits she might be haunted by guilt feelings and her relationship to men may not become the same for years to come. This is the decision the woman has to make within a few seconds while under stress and under panic and it is no wonder that the wrong decision is made many times under such circumstances, when we professionals in the field, far away from danger, are unable to make up our minds and cannot advise the women correctly in advance. One must always keep in mind that man may brandish a lethal weapon and use it in case of resistance.

It is generally known that the average rapist is a man who is not sure of his masculinity. If he were, he would not need this method to express himself sexually, he could get a partner by less violent means. In other words, he must bolster his courage in one way or another, be it alcohol, or being fortified by a weapon to "conquer the enemy," and to show the women "who is boss." In some instances the resistance the woman might offer is needed to arouse him sufficiently and to strengthen his potency to go through with the sexual act; therefore, fighting back may not deter the man but increase his aggressive behavior and also increase the danger to the woman's life. The militant women's groups advise physical resistance and are training young women in the various methods of self defense. Yet, there is the general trend among specialists to advise the women to use friendly means to persuade the attacker to let her go. Violent resistance or invectives used by the woman may only enhance his determination to have his way; a condescending attitude on the part of the woman may have the same effect.

The new freedom women are assuming outside their homes has led to a number of misunderstandings between the sexes. For instance, a woman going alone to a bar may impress some men as a sign that she was ready to be picked up, as it used to be in the "olden days," while she just wants to relax after work and is looking for some company to have someone to talk to. Or: until a few years ago Hitchhiking was a courtesy extended by a driver to someone who "thumbed a ride". Today the driver may pick up prospective sex-partners and will insist on having his way no matter how much the woman might protest. To go to a man's apartment or invite the date to one's own home was, until a few years ago interpreted as a social gesture. Today the man usually takes it as the green light to go "all the way." It is almost ironic that in our present time when women clamor for equality with men they may have to resort to the old-fashioned restrictions that were imposed on women's movements years ago or engage a chaperon (in modern language, a body guard) if they do not want to be molested or raped.

VII

In reviewing the manner in which raping took place throughout history, one can notice a definite change in its character. Raping always existed, it may even have been the customary way for a man to secure a mate. It was practiced by the tribe that was victorious in a fight with another tribe. The winner took the spoils, including the women, just as he replenished the number of horses or cattle. Raping expeditions were arranged when illness diminished the number of women of child-bearing age who were needed to secure the existence of the tribe. Nobody even considered the attitude of the woman who became the property of the conqueror; probably not even the victims themselves questioned the fate that awaited them.

For several thousands of years the Iliad has been praised as the most beautiful piece of poetry ever written and it probably is. I do not believe that it struck many people as odd that the very first verses deal with a quarrel over the possession of a young captive princess who was claimed by two of the leaders of the besiegers of Troy, Agamamnon and Achilles. Throughout history during all the invasions by intruding military hordes and wars between states to this day (including Viet Nam), the women of the enemy were the most desired and tangible rewards of the victorious soldiers. The camp followers, people of their own kind, were seduced but not raped. Laws of the various nations were very strict in protecting their female population. As a matter of fact, a man who defiled a woman of his own tribe was put to death. This severe punishment is probably connected with the rule of exogamy practiced by most primitive people. In later civilizations the various religions in conjunction with the secular rulings kept this crime in check.

While sexual assault of the women of the enemy in war time remains still very active, the shift towards raping their own kind did not assume noticeable dimensions until 10 or 15 years ago. At present, it has reached such dimensions that it endangers the safety of a woman at almost any age when on the street unescorted in the evening, or known to be living alone in an apartment or house. There must be a reason for this change and its almost epidemic growth.

The hostility toward women, camouflaged by sexual desire, is the more remarkable since the barriers between the sexes have been noticeably lowered. Not only have women become less restricted as far as their sexual freedom is concerned, but they enjoy an unparalleled upsurge in social, economic, and political aspects as well. One cannot help wondering whether there might be a connection between these two curves. In other words, women of their own kind have been taking the place of the females of the enemy.

Although there were some sporadic attempts at liberation after the women got the vote, the movement gained momentum after World War II. Up to that time virginity was a visible sign of a girl's morality. All of a sudden it lost its value and became an obstacle. After the war broke out the young men wanted to marry their girls before they were sent overseas. They got a 3-day leave and did not want to be bothered with the discomfort that accompanied a broken hymen. Pain and bleeding marred the pleasure of the young matron and put restraint on the groom. It became customary to have the hymen removed surgically a week or two before the wedding so that mutual enjoyment was not hampered by any discomfort. It served the purpose at the time, but psychologically speaking, the man relinquished his privilege of establishing his masculine superiority. The psychological consequence of this gesture is only speculative but it helped release women from the dominance of the male.

In addition, women joined the armed forces and learned to become self reliant. At home, they took the place of the men in offices and factories and Rosie the Riveter was celebrated all over the world. It surprised and hurt the masculine pride of the returning service man to find how well the women did "a man's job" and it contributed to the unwillingness of the women to return to the kitchen after the "baby boom" had had its run.

In the fifties and sixties the competition between men and women for jobs and places in politics became rather noticeable but one heard very little protest against this growing threat to their supremacy. This silence was ominous and could not mean acquiescence. Means of fighting back must have developed and it occurred to me that the parallel rise of incidents of raping their own kind may be connected with the almost same steepness in the curve of the rise of women's activities outside the home.

Against this assumption spoke at first the fact that the greatest majority of rapists belong to the economically disenfranchised part of the population as so ably described by Amir (4). They took out their grievances against women of their own kind and other less advantaged females. Their resentment is easily understandable. A great many of these grew up in a fatherless society, either being born out of wedlock or living in a broken home. In both instances there is no father to emulate or worth being emulated; the mother is the head of the household and provider for the family needs. The sisters have an easier time finding work in the categories of unskilled labor, as domestics, clerks, or sales personnel. The unskilled worker is the first to be fired in a depression and the last to be re-hired. This makes him an adult dependent on the female members of his family. He not only resents his dependency but he also has to do their bidding if he wants to eat and have a place to sleep. This dependency arouses doubt in his masculine prowess and he blames the women for causing his plight. True or not true, he thinks he would have work if it were not for this female competition. Since he cannot take out his anger on the women of his family, he takes it out on any other woman he can lay his hands on.

This does not say that raping is confined to uneducated men. On college campuses sexual assault by fellow students is not rare and here, too, their own kind are the victims. Young men between 18 and 25 furnish the largest number of perpetrators; their number diminishes with the growing maturity of the male population.

If this assumption is correct that there is a connection between sexual assault and women's progress, we must look for some indication of revolt in the other part of our masculine population. It took quite a number of years to discover the effect of women's growing independence on the psychology of their mates and colleagues. Quite a few were in favor of the woman's emergence and supported their endeavors wholeheartedly. As a matter of fact in any good marriage, the wife is a mate and often an advisor to her husband. Quite a few have always been partners with their husbands from the time they got married. A good number of men, however, still resent their wives' going to work because "it might reflect on his ability to provide properly for his family." They still feel that a woman's place is in the home and not a few women have the same philosophy. The difficulty the ERA proponents have in getting the 36 states together to pass the amendment is the best proof.

Most men try to be fair to women; they went to school with them and know that women can very well hold their own in comparison with them, but they do not really like it. Very recently some manifestations came to light that clearly express the unconscious negative reaction of men to the steep rise of women's progress in spite of their seeming approval. Among the various publications on this subject I here mention two because one was written by three male psychiatrists and one by a woman. They both came to similar conclusions about the reaction of men to the growing competition coming from women. The one is "The New Impotence" (8) written by George Ginsberg M.D., William A. Frosch, M.D., and Theodore Shapiro, M.D. It deals with the growing insecurity of males, even young ones, about their masculinity, that led to potency disturbances up to impotence. Among other factors of their concern is the fear of not being able to meet the sexual demands of their wives and girl friends. It seems that the expectation of masculine strength has been greatly overrated by some women whose main interest in their relationship with men is in sexual activity and in having orgasms instead of making it a union of two people in love who want to please and satisfy each other.

The second paper is called "Some Effects of the New Feminism" (9), by Ruth Moulton M.D. Among other difficulties in the adaptation to the new mores and social order she mentions that the sexual demands of some liberated women cause anxiety in the men that can lead to withdrawal, sexual dysfunctions up to impotence. Moreover she also reports the number of divorces in the United States has reached 50% per year.

These subtle and unconscious expressions of discontent are the weapons used by men to defend themselves against the threat to their masculine supremacy in a more delicate but equally disheartening manner than the more uninhibited male who uses rape to show the woman "who is boss." To sum it up: *The latter forces the woman to submit to intercourse without her consent; the former withdraws from sexual activity in spite of his partner's consent.* The increase in the divorce rate to 50% speaks for itself and the responsibility for the breakdown of marriage has to be put on the doorstep of both.

It is readily conceded that the radical feminists are going too far in their demands, because like any other new movement, they can not as yet distinguish between equality and dominance. They will eventually have to face reality and make concessions for the two groups of people who must live together because they cannot live without each other.

There are quite a number of other problems waiting to be solved and a great deal of research is under way all over the world. Most problems demand combined investigation by psychiatry, psychology, sociology, and economics.

Part II of this project will devote itself to trying to find answers. Some of these problems are: How to direct public opinion into the proper channels; How to instill self-respect into parents so that they will not act as pimps to their children for pornographic purposes; How to instill self-respect and respect for privacy of self and others in small children. The present breakdown of the family and the trend towards childless marriages have deep psychological reasons. Research in this direction is imperative and seems closely connected with the questions raised above.

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Treatment Outcomes as a Goal of Decision-Making

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A well-trained clinician in practice, regardless of his specialty, soon encounters unsatisfactory results in patients who have failed to respond to medical treatment or to technically well-performed surgery. The treatment program may have been based upon "acceptable" methods, but it proved to be contraindicated, ill-advised or poorly timed for that particular patient. For example, overlong persistence in a conservative regimen of expertly applied cast correction for clubfoot may result in permanent pressure deformity of the small, rapidly growing bones of the infant foot; while, on the other hand, premature intervention and performance of a well-established soft-tissue release operation may produce unnecessary scarring and rigidity. Decision regarding proper timing as to when to abandon conservatism may be a major determinant of a successful end result. Similarly, prolonged observation and hopeful, watchful waiting in congenital subluxation of the hip may extend beyond the ideal age when surgery might have been capable of producing a satisfactory result. Perhaps the most disheartening poor results are in children with cerebral palsy whose functional capacities may be marginal. An inappropriate though technically well-performed operation, may convert a child capable of limited walking with braces into an individual who is bound to a wheelchair for life.

The recognition that we, as physicians and surgeons, do not always choose wisely in selecting a management regimen or a particular operation for our patients has led to this exploration of some of the factors that play a role in decision-making, and how they are interrelated in determining treatment outcomes (1). Although every physician employs decision-making constantly and without conscious thought in his practice, and current academic interest has added very little new about the well-established fundamental principles of this approach, there is some benefit to examining the components of clinical judgment that affect our choice of how we act and intervene, and how these actions, in turn, determine the results we obtain for our patients. It is probable that better definition of the problem being considered, establishment of realistic goals, and understanding of the clinical effects of reasonable alternatives will lead to a better choice of management of patients. Keeping the objective of a proposed treatment in mind, a decision-making approach demands justification of each stage of patient management. It helps to identify when more information is needed and when there are errors in judgment. It requires that each choice be explicit and the results of each intervention be evaluated; and

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includes the patient as a major participant in choice and conduct of the treatment regimen. An inquiring approach to decision-making offers a broader framework within which physicians can make choices, identify their own idiosyncrasies, prejudices, preconceptions, routine behaviors, and those of their patients. It helps to identify factors that tend to be neglected, including benefits and costs, timing, risks, socioeconomic, family, patient selection, competence, physiological, psychological, and functional factors relating to age, and medical results as opposed to functional outcomes.

This discussion is a presentation of the approach employed on the orthopaedic service in resident and student instruction as well as patient management. The examples used, therefore, will be orthopaedic, but the principles apply to all fields of medicine. The objective is to familiarize teachers and students with the principles of decision-making as it applies to medicine by encouraging goal-oriented, rational judgment in designing treatment programs for difficult problems. Training programs that depend heavily upon the cognitive teaching of information and recall, and stress learning of accepted patterns of care, have the danger of developing a stereotyped approach to patient management, and not preparing trainees in a habit of thinking that utilizes, assimilates and evaluates new and current information, values, and personal experience into a matrix of rational clinical judgment for an individual patient, rather than solely for each syndrome and disease.

Decision-making has been used in every field of endeavor, and most recently in medicine (7, 8). The techniques have been most widely applied to problem-solving where the diagnosis is uncertain (4, 5), and recently Bunch et al (2) applied the technique to treatment and patient management. In orthopaedics, which is primarily a therapeutic specialty, the decision-making focus is more in the choice of whether or not to intervene, the selection of alternative actions, and evaluation of the anticipated results of each. Fundamentally, there is little difference between the use of decision theory in arriving at a diagnosis or selecting a method of therapy since both demand the same disciplines and require justification of each stage of the process.

Ryder (10) described the components of medical management in a Patient Care Process model (Fig. 1).

There may be many variations as to how a physician reasons and plans as he develops his own patient management program, but a Patient Care Model of this type helps to describe what steps, thoughts, and actions have been used if he desires to evaluate his own management or teach his approach to others. It demonstrates the importance of information regarding a patient, and knowledge regarding his disease, specific rather than equivocal action, realistic projected outcomes, and careful evaluation and followup as necessary components in patient management.

Arriving at a decision

At the point when a physician has processed information regarding a patient, and information regarding his medical condition and disease, he arrives at a plan for management—a decision to take a specific action. The decision-

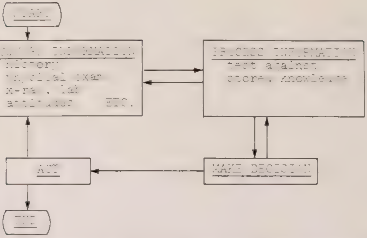


FIG 1. *The Patient Care Process Model* (Ryder) permits a visualization of the elements that a physician employs in the management of his patients. It emphasizes the interrelationship of each step, and makes clear what may be lacking in workup and information in difficult problems.

The first step is data acquisition, which follows meeting the patient, taking a history, performing a physical examination, x-rays and tests. As the physician processes this information, patterns evolve in his mind regarding possible diagnoses. He then may return to the patient to obtain further information, and at the same time, search the depths of his experiences, knowledge and the literature, or obtain consultation from colleagues to sharpen evidence and justifications. This continues until the physician arrives at the stage when he has assimilated and coordinated the information into a form he is satisfied he can use in arriving at a diagnosis. The diagnosis may be a disease, a syndrome, or a cluster of conditions with which he is sufficiently familiar to be able to outline a program of management based on his knowledge of its natural history. With consideration for the patient's aspirations and desires, he is then able to establish what might represent a realistic objective or goal. The decision he makes regarding his actions generally represents the most appropriate choice of alternatives that has the greatest probability of attaining the outlined goal with the least cost and risk. This may represent a single action or operation, or a series of sequential steps or actions. Once an action has been taken, the physician has no control over its immediate outcome, and by careful evaluation, he must decide whether the anticipated short term goals have been achieved. This evaluation represents, in effect, a new acquisition of information that describes the patient's current new condition which, again, is processed as to whether the projected course of management requires alteration. A new decision must be made whether to continue or change management until the goals or objectives are reached.

making approach, which is an analytical way of thinking, and method of evaluating clinical problems, contains many principles that every physician applies many times a day. It becomes his personal approach to patient management in the practice of medicine. Many different combinations of factors enter into his pattern of behavior in making choices and in determining his clinical judgment. Included are objective elements (i.e., knowledge and information, medical and surgical facilities, and technical capability), and subjective components (understanding and caring regarding patient needs and life functioning goals, physician attitudes, comprehension of concepts of function, evaluation, values, risks and benefits). In order to be certain that critical information and considerations are not ignored, there is benefit to an approach that identifies and makes explicit components that should be included in evaluation of the patient, and evolution of a treatment regimen. Rather than being a rigid, routine, step-by-step fixed protocol of behavior, the decision process we have employed has included a series of approaches designed to encourage goal-oriented program planning for a patient, to include followup and evaluation, and avoid errors of omission. In a similar manner, an airline pilot employs a checklist to be sure that his plane becomes airborne, but within the limits of accepted rules of flying, physical limitation of his equipment, and his own competence, his personal freedom permits a wide choice of actions and flight plans to arrive at a personally selected destination. This discussion will outline the considerations and techniques employed on the orthopaedic service as the framework for each trainee to evolve his own technique of decision-making for use in practice in the future. In addition to training, we believe the method contributes significantly to improve patient care.

Fundamental to the principle of decision-making is that the commitments that evolve are dynamic and constantly changing, and valid only at the moment for a specific set of circumstances, for a particular patient, at a specific stage of his disease. The decisions are not "engraved in stone," and should be dated to permit a documentation of the thought processes and justifications for the choices made at that particular time. When included in the patient's medical record, decision notes identify the reasons for actions that are frequently unclear retrospectively from chronological entries.

In orthopaedics, as in most fields of medicine, there may be different treatment techniques capable of achieving similar desired outcomes. Routine application of treatment methods and operations that intrigue us, and which we perform well, may not always achieve the same result because of the many factors that make each patient's individual problems different.

Making the appropriate decision is the focal step in the Patient Care Process, and fundamentally (Fig. 2) depends upon:

Definition of the problem
Exploration of alternatives or options for treatment
Choice of the best alternative

Definition of the Problem

The patient's real problem may not be represented solely by his presenting complaints or the specifics of his diagnosis. In simple situations (i.e., a nondisplaced greenstick fracture of the radius in a child) the problem is obvious, as is the expected outcome, and any one of a number of time-tested treatment techniques may be equally effective. When complex symptoms and signs

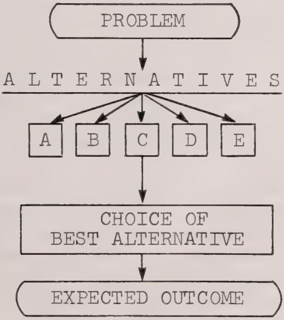


FIG. 2. Components of the decision-making process.

represent manifestations of a single disease process (i.e., tuberculosis with multiple foci) which is amenable to treatment, the major problem may be eradication of the disease (in addition to whatever management of local manifestations might be required). When a generalized condition is not amenable to specific treatment that will eradicate the disease, the "problem" may be the incapacitating clinical symptoms and signs rather than the disease itself. For example, in generalized osteoarthritis with severe hip involvement, although knowledge of the nature of the process is essential (i.e., degenerative vs. infection or tumor), the problem is not eradication of the disease itself, which is currently impossible, but the management of the pain or incapacity it creates. Pain and disability have large psychological components which must be taken into account in evaluating the functional significance of any medical condition. Psychological dependency, and hidden psychological or financial benefits of disability, for example, may represent the true "problem" rather than the patient's expressed complaints.

Why did a particular patient seek consultation advice and treatment? Was it the annoying pain in his back that brought him to the physician, or was it his fear of tumor, incapacitating arthritis, or concern that it was a sign of deterioration and aging? Does the patient identify his pains and symptoms with others who have died or been incapacitated with similar complaints? Is he in your office at the insistence of his general physician or family, contrary to his own wishes? Or do his complaints genuinely represent a problem that interferes with the quality of his life? If you are not the first consultant, why did other competent specialists fail to satisfy his needs? Treatment of the symptoms without reassurance regarding these motives for seeking opinion will not satisfy his consultative searching.

Patients often hide fundamental information about themselves, and contrarily, they are often knowledgeable as to symptoms, diagnosis and available treatment sufficiently to be able to construct a presentation for the purpose of convincing a physician to pursue a specific course of treatment. It is not uncommon to see a patient who is anxious to "get it over with," or who has special work demands and needs, defy nonsurgical treatment which was designed to relieve symptoms (i.e., bedrest, back support and exercises for a herniated disc and sciatica), and develop the symptoms that he knows would justify the surgery he seeks. The basic question remains, how can we obtain critical necessary information as to the fundamental problem which may be hidden beneath the presenting history and physical findings?

No two individuals exhibit the identical manifestations of any condition at similar stages, or to the same degree of severity, nor do they respond identically to any specific treatment. Further refinement of the "problem," as it relates to a particular patient, therefore, demands that the elements that comprise the personal profile of an individual must be tested against his medical condition. A list of variables, including age, sex, duration of symptoms, other related conditions, family and genetic history, psychological and socioeconomic factors, modify the medical condition so that it can be defined more specifically in terms of the patient's individual taxonomy, permitting a better estimate of probable outcomes of various interventions, or of no interventions at all. Since the outcome of each sequential action introduces new factors that may alter the condition at any stage of treatment, it is essential to incorporate elements of feedback in an evaluation as to how these changes, or "outcome variables," modify the current condition. Regardless of whether a patient's medical condition is of known or unknown etiology, or is a specific disease or a syndrome, the problem he presents is expressed by specific clinical manifestations, the elimination of which represents the desired outcome or goal of treatment. The results of "no treatment" (natural history that the disease or syndrome can be expected to follow) represent the baseline or control against which the success of an outcome, as the result of an intervention must be measured. Hippocrates' admonition "never do harm to anyone" stresses the need to be fully aware of the healing capabilities of nature before attempting to improve upon a condition.

The days when patients were willing to accept blindly a doctor's recommendation because he knows what is "best" are over. Combined decision-making between doctor and patient regarding goals, values and costs of obtaining these objectives, helps to identify the role the patient must play in his recovery, and avoid the frequent unrealistic misconception that a prescribed treatment will effect a total cure.

Goal of Treatment—A clear understanding and evaluation of a patient's specific problem permits development of a working plan of management that is based upon realistic objectives, goals, and expected outcomes. For example, treatment of an arthritic hip to relieve pain and increase mobility and function, cannot be expected to fully rehabilitate an individual whose psychological life style has been built on dependence upon his handicap; nor can amelioration of the factor of pain alone return a worker to an occupation that requires a greater range of motion of a joint. Most reconstructive orthopaedic procedures deal with diseased or injured parts, and final results generally represent degrees of improvment rather than cure. In estimating a realistic goal, the physician must be knowledgeable as to how much he can expect as a result of his intervention, and convey to his patient in advance, an appreciation for limited gains of a proposed treatment. There is need to develop techniques of obtaining critical information concerning a patient's motivation and capability to participate in his own rehabilitation program, and of establishing the type of realistic doctor-patient communications that lead to better understanding and greater confidence in the physician.

Information Base—When critical information is not readily available, or in the form he can use, a physician generally resorts to source material, be it books, journals, consultation with colleagues, or computers. Although the many factors that contribute to quality performance of a physician are not clear, it is possible that the more information that is available, the fewer will be errors and omissions, and the better will be the chance that he will make a proper decision. Simple memory or recall requires constant updating. By reading, study, and personal and shared clinical experiences with colleagues, a physician accumulates and constantly alters his information base to suit his special needs; each physician's base differing from that of his colleague's. No information or principle is absolute, and maintenance of current validity depends on a mind open to change. Data and facts alone may be of limited immediate practical value, and they must be reinterpreted constantly to become useful tools as they apply specifically to individual problems. A pattern of action that automatically rejects new ideas and information which do not fit into one's comfortable routine, and accepts only those which present no challenge, stifles intellectual growth and thwarts creative and imaginative thought. One of the objectives of resident and student education should be stimulation of a habit and attitude of inquiry demanding justification for all actions that are taken, and a concept of constant change toward information and principles even though it may be associated with a sense of uncertainty.

Accepted principles represent broad-spectrum general observations based on large numbers of experiences. Even accepted principles are models which change with new information, have exceptions, and are valid only under well proscribed and limited specific circumstances. Absolute immobilization in a thigh-to-toe plaster, and nonweight bearing, have been well accepted principles in treatment of fractures of the tibia, until recent successful development of the patella-bearing below-knee walking cast which is based on a completely different concept. An open mind in the proper application of principles, and willingness to adapt to exceptions and change, avoids routine thinking and rigidity in medical practice.

In orthopaedics, as in most medical specialties, the amount of information that is immediately available or applicable to a particular patient's problem is generally limited. Many descriptive facts in history, physical examination and laboratory tests may be available, as are many data in articles and case histories in the literature, but there is relatively little information that is in a form that is immediately helpful and applicable to treatment and management of the individual problems of a specific patient. Taxonomic information regarding a patient's personal profile, processed in conjunction with information stored in a physician's mind and in the literature, must be analyzed as to its meaning for each patient before it becomes of practical use in making a clinical decision.

When there is little or no information available regarding a condition or outcomes of various methods of management, a physician calls upon one of the most important aspects of his information base, namely, his clinical judgment (3) and experience (the "art" of medicine). Judgment as to which principles, bits of available related information, recall of similar circumstances in the literature, past experiences, personal preferences, opinions of respected colleagues, etc., he will employ, generally represents the basis for action in clinical medicine. Use of decision theory can help to identify fundamental available information regarding conditions and their outcomes to avoid omissions and errors. Minimizing uncertainty as much as possible by reducing questionable factors about which information is available in the literature, but often not immediately remembered, or by clarifying the relationship of variables by the use of a decision technique, sharpens and simplifies the problem upon which clinical judgment must focus. In a training setting, these principles can be introduced didactically, both for personal assessment of one's own management and in demonstrating it to others, by role models of knowledgeable instructors.

Learning how to read and interpret information in the medical literature, and evaluate reports should be one of the major objectives of a medical school and residency training program since journals and books are principal means of continuing education. Well-analyzed monographs and review articles frequently summarize the current state of knowledge of a particular subject, but few individual articles, by themselves, contain authoritative information that can be considered absolute hard facts. Although some well-written reports of carefully considered clinical investigations employ reliable statistical methods and information, numbers of cases are often too small, end result evaluations too vaguely and broadly categorized (i.e., poor, fair, good, excellent), and cases treated are of different taxonomic nature with varying degrees of difference in their stages of disease. In attempts to write complete presentations, authors often "lump" patients with varying degrees of differences, procedures performed with frequent variations (and often by different surgeons), and broadly related outcomes. An analytical physician must search for similarities, differences, inconsistences and contradictions between reports to arrive at a framework that he can use as part of his personal information base, and be prepared to alter his approach as new information appears. Publications become more meaningful, currently and for prospective clinical investigation, if completely analyzed detailed taxonomic information of treatment and evaluation is included. A decision-making approach demands critical information and evaluation, and may sharpen the ability of students in their training to read as well as write more valid medical publications.

Orthopaedics presents an additional difficulty in that, primarily as a therapeutic specialty, rehabilitative and habilitative end results can be measured only over long periods of time, frequently a lifetime. The success of a new operation to create an acetabulum in congenital dislocation of the hip in early childhood cannot be evaluated fully until later adult life, nor can the durability of a new joint replacement (and the body's response) be determined on the basis of a short-term followup of several years. The long-term significance of specific information is frequently in doubt. It is surprising to read initial reports of operations, including joint replacement devices, in the commercial advertisements of manufacturers, with no followup, before published in the scientific literature.

Internal derangement of the knee is an example of a condition in which the principles of treatment have been accepted for over forty years, but where new information, as a result of late followup studies, has created significant confusion. A torn retained medial meniscus classically has been demonstrated as a factor in the development of later localized degenerative arthritis. Recent reports of menisectomies up to forty years later, have indicated a high incidence of degenerative change in the compartment from which the meniscus was removed. Menisectomy may not be a completely innocuous procedure since biomechanically, the meniscus has been demonstrated to be a weight-bearing structure and not merely a space filler. The question is what degree of meniscus derangement is more, and what is less likely to produce the outcome of degenerative change that occurs as a result of menisectomy? What degree of tear requires menisectomy, and what tears can best be left untreated if symptoms are minimal? Arthrography, which has recently been developed to a high degree of skill has further complicated the problem. When in doubt clinically as to whether a tear exists, or to what degree, arthrography might be helpful in identifying the type, location and severity of the lesion. At autopsy, or surgery of the knee for other purposes, it is not uncommon to observe meniscus tears. Since there is no valid information regarding the number of normal individuals that have some degree of meniscus derangement without symptoms, nor the arthrographic picture of nonsymptomatic knees, the clinical and functional significance of a "positive" arthrogram remains unknown. Heavy reliance on this test has influenced clinical choices to the extent that, for many orthopaedists, a positive arthrogram represents the major indication for menisectomy.

Consideration of Alternatives

This implies an objective evaluation of all possible options for management in order to avoid preconceived and prejudicial choices. The basic alternative is always "no treatment." Against this frame of reference of the natural history of the disease untreated, all interventions and risks must be measured. In general, a treatment that does not improve upon the expected outcome of the condition untreated is of low value and introduces risk of morbidity. In many instances none of the accepted available alternatives may be expected to produce a satisfactory result. Under these circumstances, inquiry as to the components that might "theoretically" be effective if they were available, may help to clarify fundamental requirements for future clinical and experimental research.

Choice of the Best Alternative

This is the critical step in the decision process, implying that the action selected will be expected to most nearly approximate the desired outcome. Although the first step in management may be the only major step taken (i.e., a definitive surgical procedure) it is frequently only one of a series of sequential steps aimed at a desired goal. The consequences that result from each action must be evaluated in terms of how well the action accomplished the expected outcome, and whether alterations may be required in the overall program regarding future steps. Each action, therefore, produces a new condition, and new variables, and offers new alternatives which must be evaluated as to whether better choices might be available for the next sequence. Constant reevaluation is an inherent element in the decision process. Failure to obtain an expected outcome as reported by others, may be the result of the wrong indication (having selected the wrong patient for the procedure employed), the wrong operation, or the correct operation performed the wrong way.

The element of "timing" may be critical in choosing a treatment alternative. In an emergency, the choice may be made largely on the basis of immediate recall of information and past experiences. Analysis of the results of emergency actions, and exploration of consequences of other choices that might have been made, may improve future management. Review of emergency episodes for student analysis by the decision approach are helpful in teaching principles of alternative choices.

If time is not a major factor, short-term, limited objective, low-risk, often palliative management steps, aimed at alleviating elements of a condition, or a number of its more troublesome manifestations, may be justified. Frequently, a patient may not be ready for an operation or a hospital; and if palliation and temporization are not dangerous, and will not materially jeopardize later results, time may be on the side of the patient. It may be associated with some degree of spontaneous improvement, permit adjustment to a troublesome but not dangerous condition, or allow consideration of value factors that might permit a more mature and wiser decision later. A decision to defer treatment implies that a physician is aware of danger signs and symptoms that might indicate worsening of that condition, and that he outlines a program of observation and regular evaluation. The principle of "fail-safe" is fundamental in all decisions to defer treatment. It is generally justifiable to procrastinate in performing a definitive operation in order to test the effect of a conservative approach up to the "point of no return," namely, when the original proposed procedure can no longer be expected to produce a satisfactory result. For example, since total hip replacement in the adult substitutes the entire joint, reasonably similar results can be expected in a wide range of hip deterioration. In children, on the other hand, failure to recognize worsening of head-acetabular relationships in conservative treatment of congenital dislocation of the hip may jeopardize the capacity of a satisfactory outcome from acetabular surgery.

Since there may be multiple and interrelated problems, it is essential to establish priorities and weigh the importance of each problem and action individually in terms of the way in which it might condition sequential outcomes.

Value may be described as the benefit to a patient of obtaining a particular outcome in terms of the costs involved (i.e., risks, pain, hospitalization, loss of time, possible limb shortening, loss of motion, emotional and psychological trauma, socioeconomic and financial factors, etc.). Generally it is unwise to elect a particular procedure with a high probability of a successful outcome because of the surgeon's personal skill alone, if that outcome is not of benefit to the patient, or might jeopardize his life or functional capabilities. A surgeon, more adept at hip fusions than joint replacements, may be successful in relieving pain by arthrodesis, but that technique would be an inappropriate choice of alternatives, and would increase disability for a patient whose vocation requires that he sit for long periods of time.

Value, as estimated by the physician, represents what he believes to be a patient's needs, desires and purposes in seeking medical help, and consenting to medical or surgical treatment. Except for health or life threatening situations, in elective circumstances, the physician generally does what the patient wants (cure of disease, relief of pain, improvement of function) at a risk and cost the patient is willing to assume, and discourages treatment and procedures if the cost-benefit relationship is disproportionate. When the natural history of a condition can be predicted to lead to progressive worsening, and a treatment regimen is available, the value of nonintervention may be less than taking action. A physician has the responsibility to present to the patient an objective evaluation of each alternative, the risks of intervention, and the reasons for his recommendations. This information permits a patient to participate in the choice of the management, and at the same time to decrease misunderstanding, and minimize patient disappointment. Patients generally tend to be overexpectant regarding limited-gain rehabilitative procedures for pain and improved function, and physicians can frequently influence a patient's approach negatively by the extent to which they overemphasize low risks and dangers (i.e., death, cardiac arrest, thrombosis and embolism, amputation, etc.). Significant judgment is involved in communicating a realistic understanding of the benefits, purposes and risks of a proposed treatment (informed consent).

Risks—A risk may be considered in terms of the odds, chances, or probabilities of an unsatisfactory outcome taking place as a consequence of a specific action. If a course of action is chosen in the face of low probability of obtaining the expected outcome, a physician may be considered to be taking a greater-than-average risk, while the reverse would constitute avoiding risk. Most people, physicians not excluded, have a tendency to be either risk-takers or risk-avoiders. A bold surgeon, for example, may tend to "try" newly described procedures more readily than one who is conservative, and may be more likely to recommend a treatment program which, if successful, might produce better results at a higher risk. A more moderate risk-avoiding orthopaedist may trade a somewhat less perfect outcome for one affording more safety, and might choose a more conservative alternative. Recognition of one's own personal tendencies as a risk-taker or risk-avoider, and then careful evaluation of the same characteristics in a patient, may be helpful in arriving at a realistic course of action that is appropriate to the physician's capability and the patient's needs and desires.

Restrictive personal values of a physician may prevent him from appreciating those of his patients. The sedentary physician, compared with one who is athletic, may be less likely to recommend elective surgery for a shoulder that dislocates on a backstroke in an enthusiastic swimmer, and might, instead, recommend giving up the sport. Personal characteristics that may jeopardize rational decisions include stubbornness and resistance to changing a sequential course of action in the face of adversity and error, failure to recognize one's own limitation, lack of imagination, inability to adapt new information to new situations, incapacity to plan according to priorities, and failures to appreciate non-orthopaedic problems (i.e., emotional, psychological, financial, and administrative, etc.).

A patient with a restless personality who is deeply involved in a business, or way of life where rapid decisions are made all day, may treat his illness in a similar manner. His history and attitude may reflect impatience with nonoperative treatment in an attempt to influence his physician to accept a therapy program where results tend to be more rapid, rejecting a more conservative and slower approach with less risk that requires patience and personal participation (i.e., osteotomy of the pelvis or femur vs. trial of an abduction brace in his child with Legg-Perthes Disease). Fear of surgery and hospital routines, often based on lack of information and misconceptions, may prejudice a patient against accepting a preferred plan of treatment. Personality characteristics may make it difficult or impossible for a patient to choose the most ideal medical decision, and may be frustrating for the physician. However, since there is no single routine method of treatment for any condition, the goals and expected outcomes must be individualized for each patient. His personality characteristics must be considered "variables" in his personal profile, and used to construct a treatment program appropriate to his needs and desires.

Coupled with a physician's knowledge concerning the natural history of individual conditions and expected outcomes of alternative interventions, must be an underlying comprehension of the relationship of the condition to the age of the patient. In orthopaedics, physical and psychological elements as they relate to function represent an extremely important consideration. Physiological flat foot, bowlegs, in-toeing and out-toeing in early childhood generally require no treatment. Because of parental concern, it is common for pediatricians and orthopaedists to prescribe corrective shoe wedges, arches, stiff shoes, and braces. It is not unusual for parents to become overprotective when questionably effective treatment methods are prescribed instead of more time consuming reassurance, and athletic activities are unnecessarily restricted. Appreciation of the psychological aspects of growth and development serves as a framework in determining whether it is worth treating minor problems by methods that have little probability of therapeutic gain, at the risk of inhibiting unrestricted development of a child.

As new successful rehabilitative procedures are developed in early and later adult life, a future challenge in judgment will include decision as to the wisdom of performing extensive operative procedures in childhood that have questionable or limited gains in adult life. It has been an accepted principle that surgery to create a well centrated and covered hip in asymptomatic subluxation of late childhood and adolescence will probably defer later osteoarthritis. Theoretically, in the future, if the total hip replacement operation should prove to be effective for a lifetime, it might become unwise to perform reconstructive hip procedures of limited gain that are associated with long periods of disability, stiffness, and weakness for asymptomatic subluxation of the hip in adolescence, but to defer definitive surgery until the hip becomes significantly symptomatic.

In the aged, and in rehabilitative surgery in general, there is need for better knowledge of degenerative processes and their relationship to physiological function. Reconstructive surgery designed to improve the capacity of a joint may be contraindicated unless cardiopulmonary, endurance, psychological, motivational, and other functional factors are capable of responding similarly to the expected new improved condition. In older individuals, on the basis of an evaluation of the aging pattern of recent years, if visual deterioration, peripheral and cardiovascular problems, or general arthritis and debility can be anticipated in the very near future, extensive reconstructive surgery for single joint problems may not be wise. Physical restriction imposed by an arthritic joint that becomes intolerably painful only on moderate activity may be of benevolent value to an overmotivated, undisciplined patient with serious cardiac problems that call for limited activity. Physical inactivity, particularly in the aged, which interferes with the ability to care for one's self, or engage in pleasurable diversions, and is imposed by pain and joint restriction, may have serious debilitating effects both on general physical and psychological health. In healthy older persons, therefore, a greater risk factor often may be justified when the patient and his physician consider the choice of reconstructive surgery as opposed to continued nonsurgical care and increasing disability.

Each physician develops a personal style with which he is comfortable and in which he has reasonable confidence, when he approaches, evaluates, and treats his patients and their problems. The quality of clinical outcome is probably largely related to the degree of excellence of a physician's clinical judgment (3), and his expertise with an effective decision process. Even established treatment programs require constant reassessment in the light of new information and procedures. Uncertainty (9) exists as a major component in most clinical situations where information is frequently inadequate concerning etiology and natural history, alternative treatment choices and their expected outcomes, and the benefits of predictable outcomes for particular patients. Physicians who are knowledgable and experienced, and fortunate in having good intuition, frequently feel confident in their ability to make decisions in the presence of significant degrees of uncertainty, while those who are uncomfortable under these circumstances may avoid uncertainty and risk, limit their choices to more certain alternatives, and tend to become overconservative. The best choice of alternatives, therefore, cannot always represent the procedure with the least risk. When there are significant potential benefits of a particular treatment alternative, wise assessment of values and risks by the physician and the patient may justify minimizing the relative weight of the risk factor.

Methods

On the orthopaedic service, the application of a number of formal decision-making techniques has been helpful both in patient care and in translating management approaches to students and residents. As an exercise in workup of patients, and evolution of a treatment regimen, it provides a graphic visualization of the considerations and thought processes that go into making a decision, and permits critical evaluation prior to beginning treatment, during sequential stages of care, and in the followup reevaluation of the benefits of treatment. Decision-making techniques can be employed as complete patient protocols, or as segments of patient management when one is uncomfortable about a particular step in treatment, or in arriving at the best choice of alternatives.

Judgment, which we all prize as our own unique and personal capability to make the right choice of treatment alternatives, is often considered to be a

Has a Slipped Epiphysis occurred on the second side?

	NO SLIP	SLIP
DO NOT OPERATE	GOOD OUTCOME .25 x 100 = 25	POOR OUTCOME .25 x 30 = 7.5
OPERATE	GOOD OUTCOME .25 x 100 = 25*	GOOD OUTCOME .25 x 100 = 25

* - minus minimum risks and costs
of pain, morbidity, etc.

P = Possibility of bilateral slipped epiphysis = .25
V = Value of a good result = 100
Value of a significant slip or poor result = 30
P x V = E.V. (Expected Value)

FIG. 3. Example of use of a decision matrix to clarify a step in clinical management.

A 13 year old male who presents with a confirmed mild slipped proximal femoral epiphysis on the right, complains of pain on the left side as well. Symptoms and examination are clinically suggestive of a slip on the left second side, but there is no xray confirmation.

Problem: Surgery has been performed to fix the mild right slipped epiphysis with three Knowles pins. What are the alternatives for management of the suspected slip on the opposite side, and what is the best choice of management?

Information Base:

1. A minor slipped epiphysis is generally associated with little or no late sequelae, provided no further slip occurs.
2. A minor slip may suddenly become major, spontaneously, without clinical warning.
3. A major slip may produce severe lifelong degenerative changes.
4. Surgical fixation has little risk and is effective in preventing further slip.

Probability: The probability of a bilateral slipped epiphysis is 25%

Value: A minor slip that is fixed with Knowles pins generally results in a relatively normal hip—Value: 100. A severe slip generally results in later degenerative changes Value: (depending upon degree) 10–50 (arbitrarily 30).

Expected Value (PxV) Probability of bilateral slipped epiphysis (.25) x value of a satisfactory (100), versus an unsatisfactory (30) result.

a) Little or no slip: Probability of bilateral slip (.25) x value of a satisfactory result (100) = 25
b) Severe slip: Probability of bilateral slip (.25) x value of an unsatisfactory result (30) = 7.5

The treatment method that should be avoided, which results in a poor outcome with the lowest expected value is nonsurgical. Surgical fixation, therefore, generally represents the best choice of alternatives.

spontaneous response, based on a combination of experience and inherent intuition, which we feel confident will result in the best possible outcomes for our patients. It may be well to separate judgment that we use in preliminary stages of decision-making from that used in making a final choice of alternatives. Since the first two steps of the decision process are concerned with (1) definition of the problem, and (2) consideration of alternatives, errors, omissions, misconceptions, and premature interventions can be minimized by critical decision analysis during this phase of reasoning, so that final clinical judgment regarding (3) choice of the best alternative might be of the highest quality. Early in the patient care process, when there is great uncertainty, and many possibilities for diagnostic treatment options, clinical judgment can be expected to be less reliable than later in a well-designed decision process when some of the possibilities have been eliminated, and others have been converted to measurable probabilities.

The two essential tools in employing the decision process are an evaluation of (1) *probability* and (2) *value*. The general reaction to the necessity of assigning cardinal or unit figures and estimates to probability and value often prejudices a physician immediately against the use of these methods. But assigned numbers are not exact, and in fact represent a physician's judgment as to how probable it is that he can personally attain a desired outcome; and on the basis of available information, and in his and the patient's estimate, how important are the benefits in terms of this evaluation of the risks. Without using a formal decision process, a physician makes these estimates anyhow, automatically in his mind, as he chooses methods of treatment. Assignment of graphic units, therefore, does not detract from his personal clinical judgment, but in fact sharpens it, and makes it more precise, allowing him to see what he is doing and translate it to students and colleagues.

1—*Probability* may be defined mathematically as a number of occurrences (incidents, successes, complication, etc.) in relationship to the number of observations (total number of cases). From the practical point of view, in clinical decision-making, probability is the degree of belief that one has that a given outcome will result from a particular action or intervention. Barring major unexpected complications, a physician is generally able to develop a reasonable evaluation of the probability that certain common experiences will occur (i.e. technical success of surgery, infection, phlebitis, hospital days, expenses, etc.). Graphic designations of probabilities in the form of estimated percentages permit circumstances to be dealt with and modified in relationship to other elements in the decision process.

Outcomes in orthopaedics can be divided into two major areas:

1) *Technical accomplishment* of the intended outcome as a result of surgical or conservative management.
2) The *human value* or practical *benefit* of that outcome to the individual patient.

The probability of obtaining a technical goal in orthopaedics is a summation of probabilities of both positive desirable and negative undesirable outcomes. Desirable outcomes, which may have high probability because the surgeon has had excellent past experiences and results, must be weighed against his estimate of the probability of undesirable outcomes (thrombosis and embolism, infection, long posthospital rehabilitation, etc.).

The *cost* of undesirable outcomes include:

a) The *price* a patient may have to pay, including loss of time, hospitalization, pain, expense, etc., which may be inherent in the nature of the proposed operation or treatment.
b) The *risk* of undesirable events in an otherwise uncomplicated course (death, infection, amputation, thrombosis and embolism, worsening and incapacity, etc.) which might jeopardize the outcome itself.

Probability or *expectancy* of obtaining an intended outcome, therefore, must include an estimate of a physicians ability to obtain a technical outcome, from which are subtracted the costs (price and risks) that might jeopardize an uncomplicated course. For didactic purposes, different alternatives may be compared. For example:

a) A surgeon familiar with a tibial osteotomy and using internal fixation without a cast expects a 95% probability of obtaining a technically good result. Infection risk in his hospital in his hands for major surgery is 3%; anesthetic and medical complications 1%; knee stiffness of significant degree 5%; embolism 0.5%; others 0.5%; making a total of 10% complications. Of these, residuals of a permanent or serious nature may be 5%, making the overall probability of an intended outcome 95% minus 5% (costs) or 90%, taking into account unmeasurable human elements of pain, loss of time, absence from family, etc.

b) Another surgeon, unfamiliar with the procedure, performing it for the first time, and employing a cast which necessitates twelve weeks of immobilization instead of immediate motion and exercises by the internal fixation method employed above, might expect an 80% probability of obtaining a good result technically. The infection rate and risks and complications above may still be 10% (or 5% of a permanent nature). In addition, however, significant knee stiffness and increased chance of thrombosis because of prolonged immobilization would be greater, adding an estimate of 10% complications. His overall estimated probability might then be 80% minus 15%, or 65% probability of obtaining a technically good result.

2—*Value*: Costs, on the one hand, and value on the other are often used interchangeably; and in economics, they may be more closely related than they are in medicine. In orthopaedics, where the objective of a surgical or conservative management regimen is generally rehabilitation to improve function, or to relieve pain, the successful accomplishment of a technical outcome at low risk and cost may not always be of practical value, benefit or utility to a particular patient's individual needs. For the purpose of discussing decision-making processes, we have defined *value,* as the *benefit* or *utility* that a particular outcome (if successful) will be to a particular patient. If the problem is pain, can the procedure be expected to relieve him completely (i.e., arbitrary unit rating of 10), or partly (rating of 5–10), or minimally (rating of 1)? These ratings must be modified on the basis of longevity of the results since many procedures that produce good initial results (i.e., osteotomy of the hip) frequently do not continue to be satisfactory during ensuing years.

If a patient requires mobility of a knee or hip, the minimum range that he requires may be designated as a high unit rating, whereas an unacceptable range for his activities of daily living would be of low value (in spite of a technically successful operation, uncomplicated course, and low costs). Family, socioeconomic, psychological, lifestyles, dependency, litigation, vocation and other major elements of function, pain and quality of life must be weighed similarly.

In estimating *Expected Value*, from the clinical and functional point of view, when a number of alternatives can be anticipated to have different outcomes, we consider both the technical *Probability (P)* of accomplishing each intended outcome, (technical probabilities minus costs) and *Value (V)*, (or benefit and utility) of each possible outcome to a particular patient:

EXPECTED VALUE = PROBABILITY × VALUE

In general, the alternative whose outcome will have the highest Expected Value (E. V.) represents the best choice. In most clinical situations, there is generally no need to calculate expected value mathematically, since an experienced physician selects procedures in which he has the greatest confidence (highest probability), with low costs (price and risks), that can be expected to offer significant benefit to the patient (high E. V.). When a surgeon may not be familiar with an operation that theoretically appears to be the best option, outcomes are not clear and must be evaluated from reports in the literature. Estimated weights given to probabilities, costs and risks, compared with other alternatives, can be helpful in arriving at a decision as to the best treatment choice. Assignment of relative units of measure to the elements of probability, cost, risk and value, represent a judgment in itself, and become more reliable and consistent with experience. Even when physicians use similar information and similar methods of evaluation, the weight given to each of these elements may result in widely different opinions regarding clinical management.

Visible and demonstrative methods of communicating definition of the problem, consideration of alternatives (with costs, risks, probabilities and values of each), and choice of the most appropriate alternative, represent excellent teaching examples of clinical judgment.

There are no established routine methods for the application of decision theory to clinical practice and medical education. The dimensions to which the process can be applied are limited only by the imagination of the investigator. We have employed two fundamental techniques, namely the *decision matrix* and the *decision tree* or flow chart. Both depend upon being able to assign unit weights to probability and value. The decision matrix deals with a set of circumstances at a particular moment, in an attempt to determine the relative expected value of possible outcomes. The decision tree, on the other hand, depicts patient management as a function of time, and as a sequence of actions and outcomes which must be evaluated individually, as well as in terms of treatment objectives.

The *decision matrix* can be applied as an individual phase and step in a sequential decision-making process, or independently in a management program to clarify a question as to the best choice in terms of the highest expected value (Fig. 3).

Many different types of matrix analysis are employed in mathematical decision-making techniques. In clinical medicine, we have used the matrix to determine individual steps in therapy when there is a serious question of uncertainty. When there is well established information regarding incidence and values of alternative outcomes of specific actions, it is possible to clarify the expected value of different treatment options.

A *decision tree,* fundamentally, is an algorithm (6) or a plan of strategy for solving a problem which may include both ordinary and unusual circumstances.

The basic characteristics of a decision tree are that it is a sequential and graphic expression of a problem, the current information available, and the judgment employed in terms of the thought patterns in arriving at choices regarding treatment alternatives. It permits a clinician to look at a problem in a manner that possibilities are reduced to probabilities, errors are minimized, and clinical judgments may be more realistic. Decision trees may be developed as complete models to work out complex and difficult problems, to analyze unsuccessful clinical experiences, or as teaching demonstrations and exercises to develop student and resident awareness of decision-making principles. Individual steps in the decision process can be constructed to deal with special and difficult logistical segments of a clinical problem.

The symbols employed in a decision tree may vary greatly, but most conform to a simple model (Fig. 4)

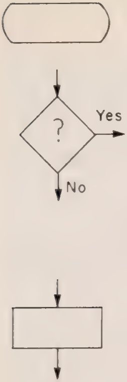
Fundamentally, there are two types of decision trees, the *programmed* and the *probabilistic.*

A—*Programmed Decision Tree:* The greater the available information, experience and knowledge, the more accurate can be a prediction regarding the probability of an outcome. When fundamental principles are well established, and all actions worth considering have been selected for a particular condition, free of judgmental elements to the extent that it is accepted practice to respond to a given condition by a particular action, the process is considered programmed. The programmed model has great usefulness as an educational technique and an outline of directions for medical assistants and health professionals (11). When an institution, director or service, or health care program requires that emergencies or special problems be managed in a particular manner, a programmed decision tree or algorithm may be constructed. There must be safeguards consisting of referral to a responsible medical or professional individual for judgmental decisions when unusual non-programmed responses or conditions are encountered (Fig. 5).

Programmed models have the danger of becoming fixed and routine, and as an educational tool may convey the sense of authority. They must be reevaluated constantly. The utility of a programmed model depends upon maintaining current the validity as to what action is appropriate for each given condition.

B—*Probabilistic Models,* which represent the major number of clinical circumstances, differ from programmed models in that they deal with significant uncertainty regarding unavailable information about the medical condition being treated, and predictable outcomes of alternative interventions.

The ability to construct a probabilistic tree depends upon development of weighted units of measure to designate both a physician's personal estimate of probability (including costs and risks), and the values of each outcome of alternative interventions. Rather than an objective mathematical determination, it is a personal judgment of the confidence of a physician to accomplish stated objectives based on experience, knowledge of principles, intuition, and subjective elements of prejudice, misconception, clairvoyance, guess and hunch. While we are generally comfortable with more objective evaluations of risk and cost, the human element of value demands wise clinical judgment in



---Start: Problem or diagnosis

---End: Desired Outcome

---Branch Point: Generally contains a question concerning the presence or absence of a condition, the answer to which determines one of two, or several, possible courses

---Action: (i.e. surgical procedure) Once an action has been taken, a period of time must elapse to observe and evaluate the effects of the action, before the next sequential step is taken.

FIG. 4. Symbols employed in a flow chart or decision tree.

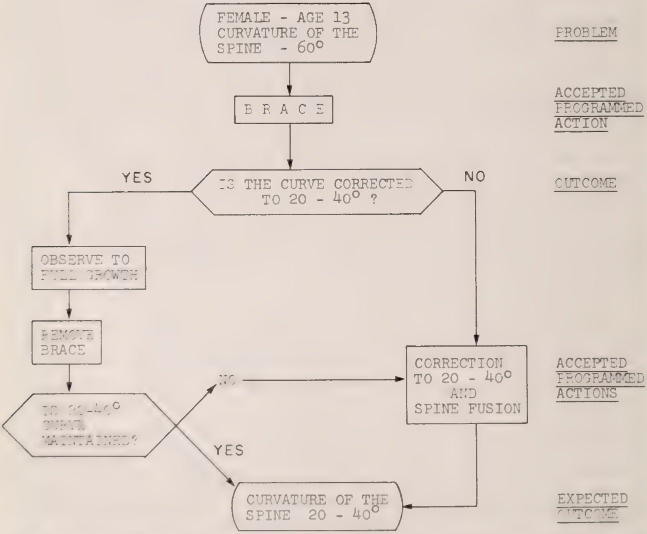

FEMALE - AGE 13
CURVATURE OF THE
SPINE - 60°
PROBLEM
BRACE
ACCEPTED PROGRAMMED ACTION
YES
IS THE CURVE CORRECTED TO 20 - 40° ?
NO
OUTCOME
OBSERVE TO FULL GROWTH
REMOVE BRACE
IS 20-40° CURVE MAINTAINED?
NO
YES
CORRECTION TO 20 - 40° AND SPINE FUSION
ACCEPTED PROGRAMMED ACTIONS
CURVATURE OF THE SPINE 20 - 40°
EXPECTED OUTCOME

FIG. 5. *Programmed Model.* Illustration of a programmed model to demonstrate to students the fundamental considerations in management of idiopathic scoliosis. In this model, the physician has indicated that a curve of 20–40° is acceptable. Individual variables (patient profile) may introduce uncertainty and probabilistic elements into programmed models, requiring clarification by consultation or obtaining further information. In addition, value (i.e., cosmetic appearance) and functional (i.e., cardiopulmonary capacity) features are often important considerations.

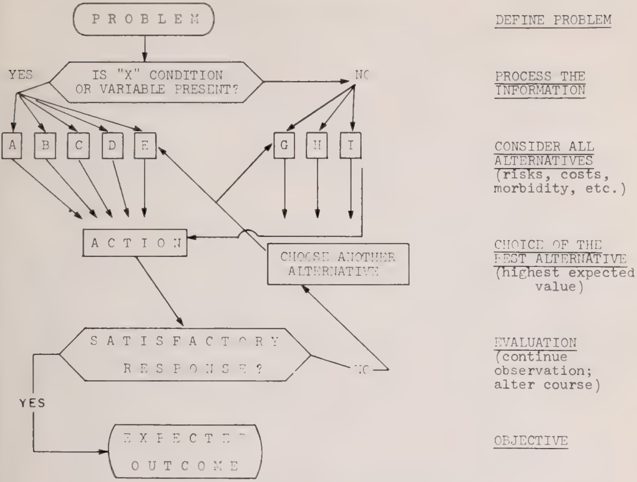

PROBLEM
YES
IS "X" CONDITION OR VARIABLE PRESENT?
NO
A
B
C
D
E
G
H
I
ACTION
CHOOSE ANOTHER ALTERNATIVE
SATISFACTORY RESPONSE?
NO
YES
EXPECTED OUTCOME
DEFINE PROBLEM
PROCESS THE INFORMATION
CONSIDER ALL ALTERNATIVES (risks, costs, morbidity, etc.)
CHOICE OF THE BEST ALTERNATIVE (highest expected value)
EVALUATION (continue observation; alter course)
OBJECTIVE

FIG. 6. Probabilistic Model Flow Chart.

establishing relative estimations in order to arrive at a selection of realistic individual and personal treatment alternatives (Figs. 6 and 7).

Conclusions

A decision-making approach to patient management is a method of systematic thought which permits rational utilization of information derived from study and experiences to formulate a course of appropriate clinical judgment for a particular patient. It permits accommodation of a new data and information in ever-enriching and reliable medical practice. A decision matrix, decision tree, or flow chart for difficult problems may be helpful as a graphic demonstration of a rational and sequential thought process which is useful in specific problem-solving and in medical student and resident instruction. It presents a graphic picture of observation, data assessment, decisions, and actions involved in patient management, which allows us to see what we are doing, since it demands justification and evaluation of each sequential step. It is a discipline that demands:

a) Specific definition of the problem of a specific patient, and evolution of realistic goals or objectives as expected outcomes. All variables that describe the individual taxonomy of a patient in relationship to a particular disease are essential in the specific definition of his individual problem;
b) Construction of an information base, which contains both knowledge

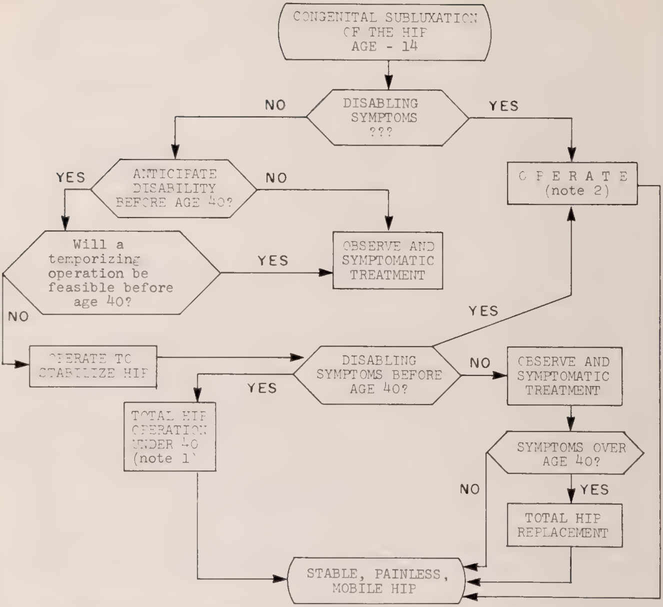

CONGENITAL SUBLUXATION OF THE HIP AGE - 14
DISABLING SYMPTOMS ???
NO
YES
ANTICIPATE DISABILITY BEFORE AGE 40?
YES
NO
OPERATE (note 2)
Will a temporizing operation be feasible before age 40?
YES
NO
OBSERVE AND SYMPTOMATIC TREATMENT
YES
OPERATE TO STABILIZE HIP
DISABLING SYMPTOMS BEFORE AGE 40?
YES
NO
OBSERVE AND SYMPTOMATIC TREATMENT
TOTAL HIP OPERATION UNDER 40 (note 1)
SYMPTOMS OVER AGE 40?
NO
YES
TOTAL HIP REPLACEMENT
STABLE, PAINLESS, MOBILE HIP

FIG. 7. *Probabilistic Model:* Congenital Subluxation of Hip, Age 14. Reconstructive surgery of a subluxated hip at the age of 14 is generally not successful in creating a stable condition that will prevent later osteoarthritis. The decision as to whether a temporizing procedure to gain better stability and improve longevity of the hip should be performed at the age of 14 may be made on the basis of the degree of clinical disability rather than on the xray appearance.

Note (1): It has been established that total hip replacement is a satisfactory procedure for degenerative arthritis of the hip in the adult. Since the operation has been performed for only 20 years, many orthopaedic surgeons prefer to delay its routine performance to a later age group. As long term experience accumulates, and orthopaedic surgeons gain greater confidence with the operation, it may become indicated in early adult life when early disability and degenerative changes occur.

Note (2): Surgical alternatives in adolescence (estimated):

Alternatives	Probability	Value	Expected Value
Femoral osteotomy	.95	20	190
Innominate osteotomy	.90	20	180
Acetabular rotation	.60	40	240
Chiari osteotomy	.80	70	560
Cup arthroplasty	.70	40	280
Colonna arthroplasty	.30	30	90
Total hip operation	.60	95	570

The assigned figures above are for illustration only, the theoretically represent a particular surgeon's estimate of his own capabilities in obtaining a technical outcome, and his concept as to the value of each outcome to his patient. If an initial operative procedure fails, and revision is required, alternatives and expected values msut be redetermined depending upon the new state or condition of the patient.

Evaluation of surgical alternatives by the probability of each individual surgeon's capability of about the patient and about his condition, obtained from many sources and interpreted in a fashion that the physician can utilize in deciding upon a specific action;

c) Consideration of reasonable alternatives, their probability of attainment, and value to the patient;

d) Specific choice of the most appropriate alternative in terms of expected value, and outline of a program of management;

e) Evaluation of the outcome of each sequential action and reconsideration of possible new choices and changes in the course of management if necessary.

A decision tree has the inherent danger that it might be accepted as authoritative, and each step followed without evaluation and analysis. A programmed tree, which applies accepted principles and information as routine responses to common outcomes, can serve as an excellent teaching method and a guide to programs that are conducted by health professionals. If properly constructed, the programmed model implies constant reevaluation of the information base, and retesting of management outcomes, to assure that it does not become outmoded and obsolete. There is nothing more dangerous than a bad or outdated programmed decision tree.

The great deal of uncertainty that exists concerning current information and long term outcomes (particuarly of new procedures) makes the probabilistic decision-making model a more usual clinical experience. The decisions that one makes are personal, and reflect the quality of clinical judgment. Rarely does the decision tree of one physician mirror that of another. The methods employed may differ, as may the information that each physician uses in the evaluation of a patient's problems, and evolution of realistic goals and objectives. Within these parameters of differences, and their uncertainties, the decision-making process permits maximum consideration of the elements of probability and value, and helps to minimize errors in sharpening clinical judgment to arrive at realistic goal-oriented management programs for individual patients.

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accomplishing a technical procedure (P) and the value of the outcome in terms of its ability to produce stability and pain relief (V) permits estimation of expected value (E.V.) for each alternative. In this model, the Chiari operation (osteotomy of the pelvis and medial displacement of the head of the femur to obtain coverage under the ilium) as an example, arbitrarily has been assigned a high expected value. In the judgment of the surgeon, if a procedure does not offer a particular patient adequate benefit, and the theoretical benefit of a total hip replacement is considered relatively much greater, hip replacement might be considered at an early age with full recognition of higher risks. The high value of the outcome and the immediate high probability of technical success of the total hip operation must be conditioned by uncertainty of longevity of the mechanical device and possible later complications because of inadequate information concerning long term results. (Therefore, a probability is assigned .60 rather than .90 in the adult osteoarthritic hip).

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An Approach to Community Health Education by a Voluntary Hospital

JAMES M. RUBIN, M.D. and PHYLLIS G. RUBIN, M.A.

In the Fall of 1973 the Committee on Community Health Education was reconstituted by the Medical Board of Beth Israel Medical Center, New York with one of us (J. M. R.) appointed as Chairman.

The Medical Board responded responsibly to fill the void in preventive health care in the local community regarding guidance and information on various health subjects. The Medical Board was cognizant that community health education is necessary in order to promote a person's ability to care for himsef more adequately and maintain health at optimal levels (1). The Board, concurring with recommendations of the American Hospital Association, believes that in the long run consumer education contributes to the most economical use of health facilities and services and believes that these programs can result in improved community relations (2).

The Community Health Education Committee had not been active since 1967–1969, during which time it had sponsored an annual series of four monthly lectures on current health subjects. The format of the 1967–1969 series consisted of one physician lecturing on his topic in the hospital auditorium, followed by an audience question and answer period. Attendance ran from 40–200 people per session.

The reconstituted Health Education Committee was charged by the Medical Board with the task of developing and implementing new health education programs for the community Beth Israel Medical Center serves. Committee members included physicians, dentists, representatives of the Nursing Department, Volunteer Service, Community Relations Department, Public Relations Department and Administration.

The committee also recognized the importance of educating the public in health matters. At the same time the committee was knowledgeable in the problems that might impede the success of any attempted program. The committee was also acutely aware of the individual needs of people within the community, recognizing a universal desire either to maintain or improve their health status. The physicians on the committee agree with Jamplis who states that lack of knowledge and understanding undoubtedly contributes to the widespread tendency of patients not to comply with therapeutic or prophylactic regimens (3).

Mindful of the tremendous amount of new material available in our rapidly advancing technology the committee realized that a program was needed

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which would organize and integrate this information; the ultimate goal being an individual's ability to make educationally sound decisions about his health.

We intend to show that a program can be devised that will be successfully attended with health information dispensed if there is

1. proper planning;
2. recognition of problems;
3. integration of hospital resources;
4. active creative publicity; and
5. cooperation of the professional staff.

The committee met on alternate Mondays for a period of six months and discussed and worked out the following problems:

The first problem was to define the meaning of the term "Beth Israel Community." In the broad sense, the committee felt that the community encompassed not only the area in which the hospital was situated but the surrounding area from which the staff drew its patients. The committee also realized the importance of adequate publicity directed toward the community within walking distance of the hospital because they felt primarily responsible for this group.

The second problem was to overcome the resistance of individuals to attend a program that would be presented at the hospital. It was decided to have the program in the Spring of 1975 in the early evening (before dark, for reasons of safety) and to mount an intensive community-oriented public relations campaign. Complimentary refreshments were to be served. The Public Relations and Community Relations staff conducted the following campaign:

1. Fliers describing the program to the people on the mailing lists of various community agencies.
2. Fliers and programs distributed to Beth Israel professional and nonprofessional staffs.
3. Notices in local newspapers.
4. Posters in the Hospital.
5. Program and fliers distributed in our Out-Patient Department.
6. Spot announcements on local radio.
7. Posters in local stores and apartment houses.
8. Telephone calls to various community agency personnel.

The third problem was to devise a format and program that would not only appeal to the potential audience but would also provide the most information to the greatest number of people and help them develop healthy attitudes.

The program that was presented on April 29, 1975 was entitled "Everything You Want To Know About Your Heart (Heart Diseases, Stroke and High Blood Pressure)." The format provided for a keynote speaker, who presented an overview of the problems to the entire assembled group. Several patients spoke at this time on pertinent medical problems. Following the keynote address the audience of 300 divided into five groups. This had been prearranged during registration and people were directed, by members of the volunteer staff, to the appropriate areas, where their groups were meeting. Each of the five groups was led by a physician group leader and assisted by two other physicians. Patients of these physicians were also present to be interviewed.

The nature of the format encouraged informality and frankness promoting a lively and candid question and answer period.

The audience reported that they enjoyed hearing patients discuss their feelings, successes and failures encountered with their various treatment or diseases. The physicians spoke on numerous diagnostic and treatment procedures, some leaders showing slides and movies. The responses tabulated by the Public Relations Department from a majority of the evaluation forms collected at the end of the program showed a favorable response to the events that had occurred. Along with several personal interviews, the comments revealed that the audience were immensely satisfied with the program, feeling more knowledgeable about such problems as heart disease and hypertension.

Before the program, all of the speakers had been briefed by the committee to present their material at a level suitable for the layman and to leave sufficient time for questions. Likewise, the group leaders were impressed by the interest demonstrated by the audience and had to exceed the scheduled time for the program. Encouraged by the response of the community to this pilot project, the Medical Board voted to conduct these Health Education Seminars on an annual basis.

Conclusions

The Community Health Education Committee concurred that they met the goals that were set forth. The program was very well attended by diverse factions of the community. The audience was receptive to the format, leaving with knowledge, attitudes, and literature that would be helpful in making sound health decisions. Participants observed that the facilities and resources of the Medical Center exist, not only to handle their health problems but also to teach and educate them in health matters.

The committee credits the intensive public relations and community relations campaign, the choice of topics, the format and the overall cooperation of participating professional and administrative staffs with insuring the success of the program. Plans for future programs call for keeping the same format with more and smaller discussion groups.

The Community Health Education Committee's feelings are similarly stated by the Task Force on Patient Education for the President's Committee and Health Education, that with increased nationwide recognition for preventative health care and maintenance it is imperative to have a goal of organized, planned patient and non-patient education programs. The goal is to "maintain a positive state of health, care for themselves more adequately and prevent possible recurrences when feasible" (4). The authors' feelings can be summed up by quoting the following statement: "Now, perhaps more than ever before, the individual must learn how to use resources of modern medical science effectively and efficiently. People must be helped to acquire a greater sense of personal responsibility for their health and to change many of their living habits in order to enhance their chances for a long and healthy life" (5).

Summary

It was established that there was a need for improved health education within the Beth Israel Medical Center Community. In order to fulfill this need an innovative program was devised and implemented. The dynamics of the format resulted in effective dissemination of current information on the subjects of heart disease, high blood pressure, and stroke. The humanistic approach was successful in attracting a large audience and enhancing their perception of certain personal health needs.

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Forty-Five Days under Anesthesia:

A New Treatment for Massive Ventral Evisceration

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This is the report of a patient who survived forty-five days of continuous anesthesia. The unusual therapy was employed to solve surgically insoluble problems posed by the combination of duodenal fistula, massive ventral evisceration, generalized peritonitis, and sepsis.

Case Report

The patient was a 45-year-old man who had entered another hospital for treatment of an intractable duodenal ulcer. The initial surgery, performed on October 10, 1975, consisted of a Billroth II gastrectomy (Polya gastrojejunostomy). The abdominal wall was repaired in three layers. The initial course was unremarkable. Oral feeding was started on October 14, the fourth postoperative day. Two weeks following surgery, October 24th, the patient developed violent abdominal pain with vomiting and signs of shock. Despite gastric aspiration and parenteral fluids, he became oliguric and collapsed.

On October 27th, the patient was transferred to our Intensive Care Unit with signs of generalized peritonitis.

Emergency laparotomy revealed a total duodenal leakage with 3 liters of frank pus in the abdomen, and violent generalized peritonitis. The duodenal stump was resutured and the abdominal cavity drained. The abdomen was closed in two layers. Continued shock and failure to improve required surgical intervention the next day.

At the third surgical intervention, October 28th, multiple adhesions were encountered with localized purulent collections. There was, in addition 3 liters of pus in the general peritoneal cavity. Despite integrity of the previous duodenal closure line, a tube duodenostomy was performed and exteriorized. Multiple drains were placed in the right and left lumbar gutter and the abdomen closed with retention sutures.

The postoperative course was stormy from the onset. On the third postoperative day, October 31st, the patient exhibited chills, fever, dyspnea, and signs of generalized sepsis. The abdomen continued to display the physical signs of peritonitis.

There was progressive deterioration of the clinical picture until the sixth postoperative day, November 3rd, at which time leakage of intestinal contents appeared along the sutures and drains. The patient was in a deep shock, perspiring, with a temperature of 40°C, a blood pressure of 110 mmHg, and a pulse 140/min. The patient was icteric (serum bilirubin 24 mg/l), his skin was mottled, cold, and clammy, and he was hyperventilating. Blood chemistries revealed uremia (BUN = 70) and metabolic acidosis ($HCO_3^- = 13$ mEq/l, $pCO_2 = 19$ mmHg). Three blood cultures were positive for B. coli. Gastric aspiration produced 1800 ml. The general condition of the patient was so grave that the surgical staff concluded that exitus was inevitable. Vigorous resuscitation, however, was immediately instituted and consisted of the following measures:

1. intratracheal intubation and mechanical respiration.
2. antibiotic therapy—6.0 gm/da ampicillin and 160 mg/da gentamycin.
3. parenteral alimentation by intravenous perfusion of 1600 calories/da of glucose.
4. correction of electrolyte abnormalities by appropriate I.V. fluids.

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5. treatment of metabolic acidosis and peritoneal shock with hydrocortisone 1.0 gm/da, heparin 80 mg/da, lasix 400 mg/da, and 120 mEq sodium bicarbonate intravenously.
6. treatment of peritonitis by irrigation of the peritoneum with lactic acid injected along drainage sites following Tremolieres' method.
7. neurovegetative sedation using I.V. Droperidol (dehydrobenzperidol) with automatic injection syringe of 20 ml, in a progressive manner (45 mg the first day, and 130 mg the second day).

The immediate result of this therapy was improvement of skin tone and color, slowing of the heart rate, reduction of fever, and cessation of shivering. The metabolic acidosis gradually responded and subsided after three days, at the end of which time the patient's general condition was stable (Fig. 1).

On November 5th, the lasix and hydrocortisone were stopped. Droperidol was increased. The daily doses employed are graphed in Figure 2.

On November 8th, we added Fentanyl (1-N-2 N phenethyl-4N-propionyl-anilino-piperidine) to insure deep continuous neuroleptanalgesia.

On November 9th and 10th, there was recurrence of fever and metabolic acidosis but blood cultures remained negative. The exacerbations were associated with progressive wound dehiscence. The shock and metabolic acidosis were ameliorated by the administration of 2.0 gm of hydrocortisone. The wound was isolated from the environment in a plastic tent and irrigated with lactic acid solution (Fig. 3a). By November 15th, the wound separation was complete and small bowel loops were eviscerated. They were contained with vaseline gauze. Surgical repair being considered impossible and wound approximation with elastic bands failing, vaseline dressings were continued as was lactic acid irrigation.

During the next four days the patient seemed comfortable, sleepy, the fever subsided, the vital signs and blood electrolytes returned to normal. In response to this recovery, on November 19th, the patient was taken off the ventilator, extubated, and the neuroleptanalgesia was discontinued for a few hours. On November 20th, chills, fever, shock and a Proteus-positive blood culture recurred. Intubation and neuroleptanalgesia were reinstated. Another attempt was made to stop

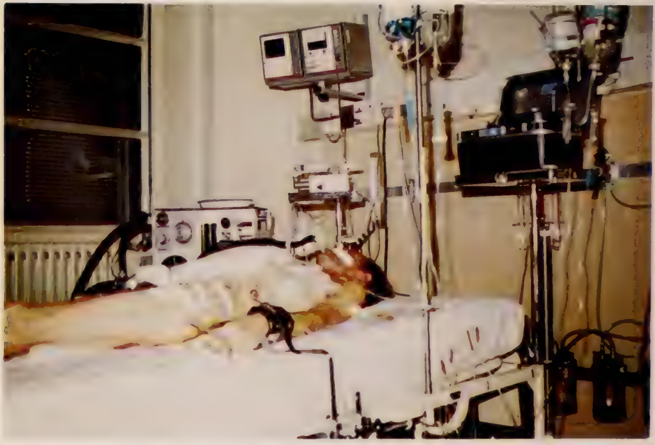
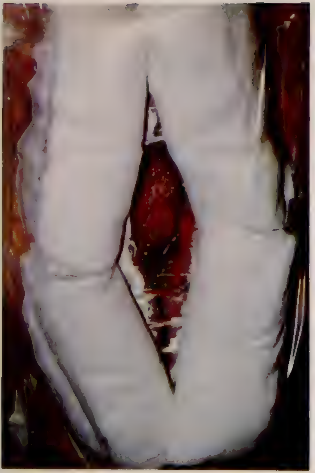


FIG. 1. The steadiness of perfusions is done through a pump which can be seen at the left side of the patient, on the table.



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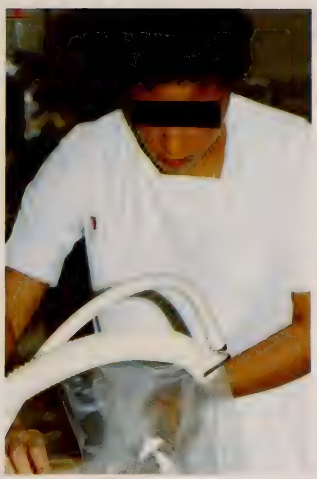

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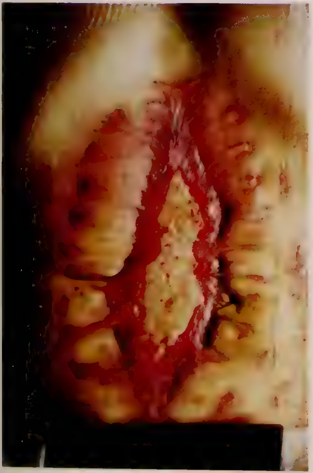

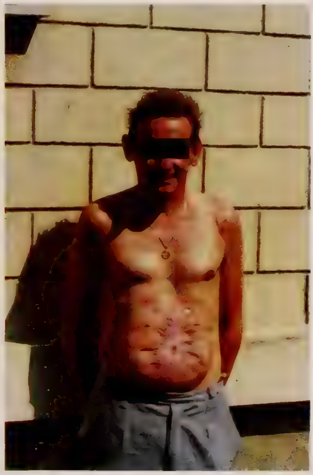

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FIG. 3a. Under the transparent plastic tent, between gauzes, we can see the median suture opening with three suture points still on. The red area is the liver; the green color near the three suture points is given by lactic acid.

FIG. 3b. Oxygen-enriched humidified atmosphere.

FIG. 4. The black rectangle on the lower part of the picture is the Karaya's gum plate which was applied on the opening in order to obtain better scar results. The cleaning of secretions was done daily (picture taken December 30, 1975).

FIG. 5. Patient ready to walk out of the hospital.

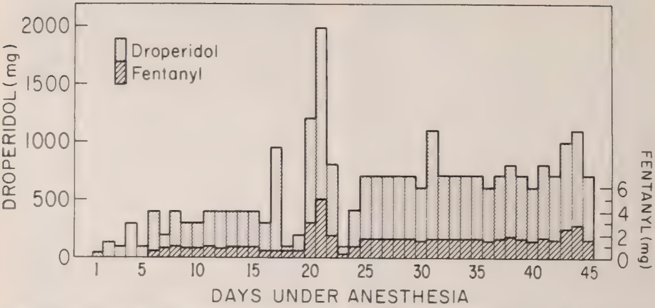

FIG. 2. Daily dosage of neuroleptanalgesia (Droperidol = dotted area; Fentanyl = black area).

these therapies four days later but was abandoned six hours later because of obvious rapid deterioration of the patient's respiration and circulation.

On November 28th, gentamycin and ampicillin were replaced by 8 million units/da of penicillin G. Locally, the wound infection appeared to be improving. In addition to continuing copious irrigation with lactic acid, on December 1st the wound tent was perfused with an oxygen-enriched humidified atmosphere (Fig. 3b). Shortly thereafter, the duodenal fistula closed and on December 2nd, the patient had spontaneous bowel movements. Feeding by gavage, 2000 calories/24 hours, was started and with continued I.V. alimentation of a mixture of lipids, proteins, and 30% glucose at 3000 calories/da, it was possible to provide a total daily intake of 5000 calories.

From this time, December 2nd, the patient began a gradual recovery, punctuated by minor problems such as:

1. brief diarrhea for several days after December 6.
2. persistence of neurovegetative stability for some time after permanent cessation of neuroleptanalgesia.
3. electrolyte problems, including low serum Na and K due to excessive loss by diarrhea and diuresis, treated with I.V. 350 mEq/da of sodium bicarbonate and with 0.5 mg synthetic ACTH for 10 days.

On December 24th, the respirator was removed. Two days later, he was extubated. By this time, there was marked improvement of the wound. The infection had cleared, the loops of bowel were firmly agglutinated, the peritoneum appeared thickened and the wound edges were being approximated with ingrowth of epithelium from the sides over the peritoneum. The irrigations were stopped, the isolation tent removed, and the wound covered with a soft plate made of Karaya's gum (Fig. 4). Improvement continued generally and locally until January 9th, when intravenous feeding and gavage were discontinued and the patient was placed on progressive oral feedings.

On February 7th, the patient stood up for the first time. He walked out of the hospital 6 months after admission. His previous digestive complaints were gone, his appetite was excellent, he had gained 6 kg. Since discharge he has been well (Fig. 5).

Comments

In this case, the leakage of the duodenal stump caused violent peritonitis, which in turn induced shock, sepsis, and evisceration—potentially lethal complications. Immediate resuscitation was successful through the use of antibiotics (for infection), steroids and alkalinization (for shock, adrenal insufficiency and metabolic acidosis) and heparin with lasix (for renal insufficiency).

The continuous neuroleptanalgesia was vital in restricting neurovegetative responses that would have been incompatible with prolonged survival. This therapy was maintained from November 3rd to December 18, 1976 (45 days) using about 26 grams of Droperidol and 60 mg of Fentanyl.

The irrigation with lactic acid neutralized the alkaline duodenal secretion and inactivated its ferments as well as mechanically washed away necrotic tissue. This enabled the peritoneum to control infection and to provide granulation tissue for repair by revascularization, contraction of fibrous tissue, and epithelialization from the skin. We believe the humidification and oxygenation of the isolated environment stimulated the development of granulation tissue. The extended neuroleptanalgesia permitted prolonged tolerance of intubation with mechanical respiration and prevented death from exhaustion, shock, hyperthermia, and hypermetabolism. Our patient revealed no evidence of intolerance, toxicity, nor other sequelae.

Conclusion

Prolonged continuous neuroleptanalgesia permitted appropriate local and general therapies to result in survival of a moribund patient who developed duodenal leakage, shock, generalized peritonitis, and total evisceration following surgery for duodenal ulcer.

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Legg-Calve-Perthes Disease associated with Hereditary Multiple Exostosis: A Case Report

JACOB F. KATZ, M.D.

Abstract

Hereditary multiple exostoses presenting in coexistence with Legg-Calve-Perthes disease in two male children have been noted.

One child studied in detail appeared to follow the usual pattern of L-C-P reconstitution. It is suggested that the Legg-Calve-Perthes disease developed as an unrelated concomitant process independent in its course and healing from the underlying hereditary exostoses.

In a previous study (1) of 358 patients, fourteen children with Legg-Calve-Perthes were found to have ten different concomitant medical conditions that did not alter the expected course of healing. These are shown in Table I and included such diagnoses as cerebral palsy, cavus foot deformity, coxa vara, diabetes mellitus, and Down's Syndrome. Crawford (2) and Markheim (3) each reported Legg-Calve-Perthes disease coexistent with slipped capital femoral epiphysis.

This report extends the variety of conditions coexisting with Legg-Calve-Perthes disease by recording its presence with hereditary multiple exostoses.

Case Report

D. B., an 8-year-old Caucasian male child developed pain in the right knee in April 1975. Two weeks later he began to limp and shortly thereafter roentgenographic examination revealed changes consistent with Legg-Calve-Perthes disease of the right hip.

He was a full-term infant, second of three children delivered without incident, and weighed seven pounds at birth. His father, 36-years-old, had hereditary multiple exostoses, as did his two male siblings. His mother, 35-years-old, and maternal grandfather had hereditary retinal degeneration. The patient had had confirmation of hereditary multiple exostoses the year prior to his present symptoms.

His initial treatment was six weeks of bedrest followed by crutch supported walking until October 9, 1975 when he was admitted to The Mount Sinai Hospital. Workup revealed normal urinalysis, white blood count 6600, polymorphonuclear cells 51, band forms 2, lymphocytes 42, monocytes 2, eosinophiles 3 and basophiles 1; red blood cells 4.3 million; hemoglobin 12.3 grams.

Local examination indicated ⅝″ shortening of the right lower limb with 30° flexion contracture, 15° loss of abduction, 20° loss of internal rotation and 30° loss of external rotation.

Roentgenograms taken in April (Fig. 1), June, and August (Fig. 2) 1975 showed progression of changes consistent with Legg-Calve-Perthes of the right hip. Minimal to moderate diminution in height of the capital femoral epiphysis and progressive fragmentation were noted. Multiple exostoses were present in greater prominence about the proximal left femur and about both knees (Fig. 3).

Bilateral long leg plaster casts with "broomstick" cross bar were applied on October 9, 1975 (Fig. 4). Satisfactory centering of the right femoral head was noted. The alternative therapies

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TABLE I

Conditions Associated with Legg-Calve-Perthes Disease

Bilateral cavus feet	1
Unilateral coxa vara	1
Mental retardation	1
Diabetes	2
Hyperthyroidism	1
Mild tibia vara	2
Down's syndrome	1
Cooley's anemia	1
Fractured shaft femur	3
Cerebral palsy	1

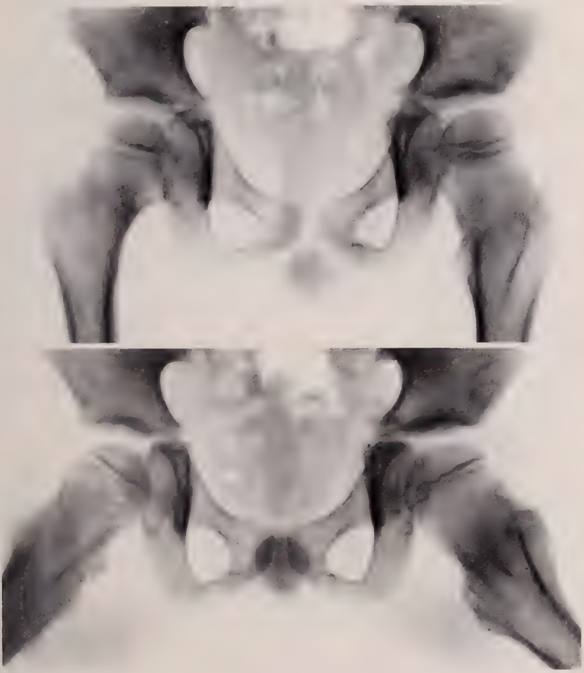

FIG. 1. These roentgenograms indicate the status of the hip joints on 4/4/75 when the early symptoms about the right hip were being investigated. The antero-posterior views are not conclusive; the frog-lateral views indicate mild diminution in height of the anterior margin of the right femoral capital epiphysis. Although exostoses are present bilaterally, the left proximal femur is more distorted than the right.

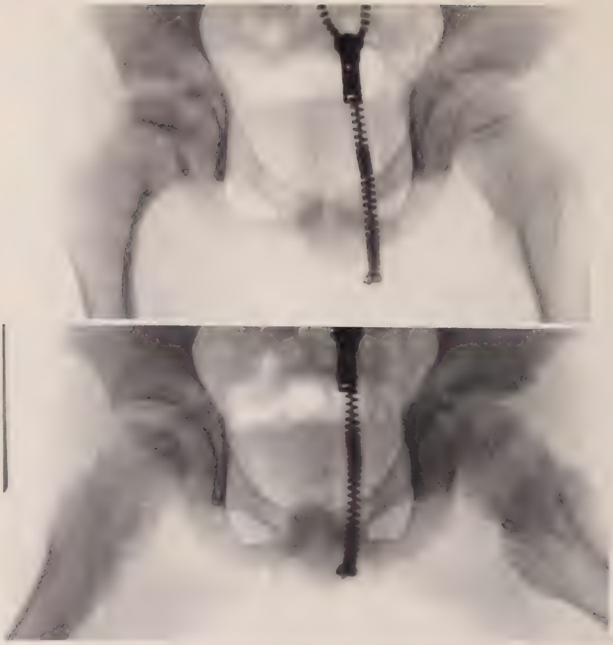

FIG. 2. These films on 6/24/75, show unequivocal changes in the right femoral capital epiphysis. In addition to diminution in height, there is subchondral lysis of the anterior portion of the femoral epiphysis as seen in the frog-lateral view.

were explained to the child's parent and it was elected to pursue a surgical approach. On October 15, 1975 varus-derotation osteotomy (Fig. 5) of the right proximal femur was performed and plaster hip spica applied.

He was transferred to the Blythedale Children's Hospital on October 23, 1975 for the remainder of his treatment (Fig. 6).

C. H. Following the above experience, the roentgenograms of a second child with similar coexisting hereditary multiple exostoses were reviewed in consultation (Fig. 7). The child's right hip was involved. In this patient both proximal femurs were equivalently affected with exostoses.

Summary

Hereditary multiple exostoses presenting in coexistence with Legg-Calve-Perthes disease in two male children have been noted. Each child had unilateral involvement, in one case affecting the proximal femur with lesser exostoses

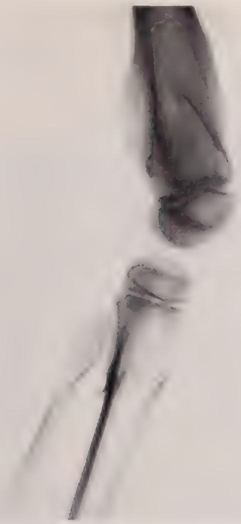

FIG. 3. This is the knee area showing representative deformity associated with multiple exostoses.

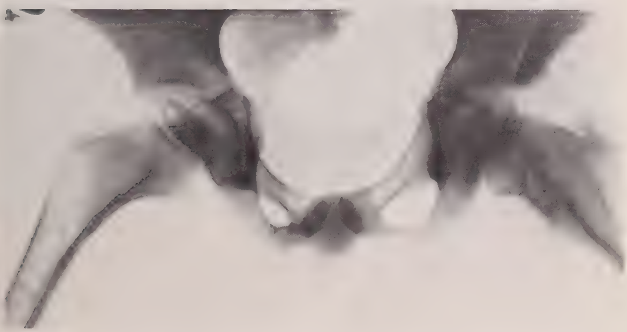

FIG. 4. This roentgenogram taken prior to surgery reflects the femoral head relationships with the lower limbs in extension internal rotation and abduction. There is adequate centering of the femoral heads with good acetabular cover bilaterally.

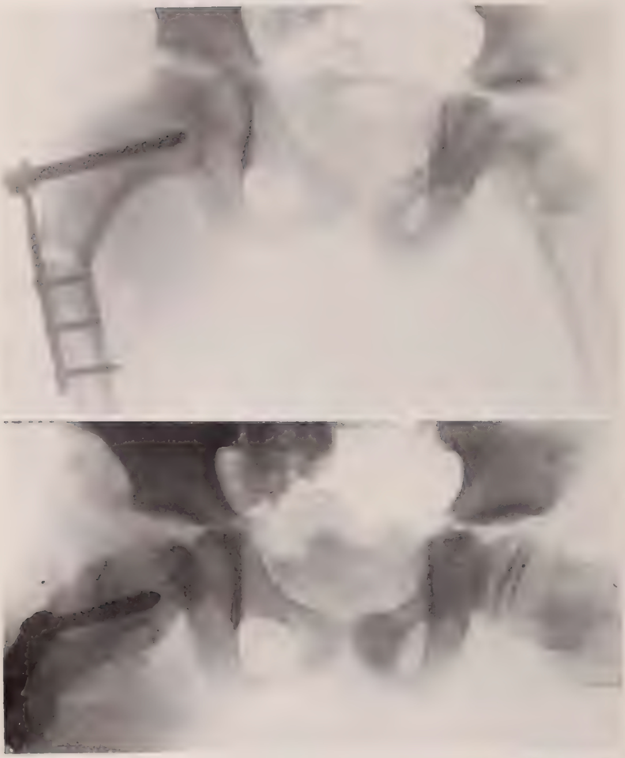

FIG. 5. These films reveal the immediate postoperative status on 10/15/75 following varus derotation osteotomy of the proximal portion of the right femur.

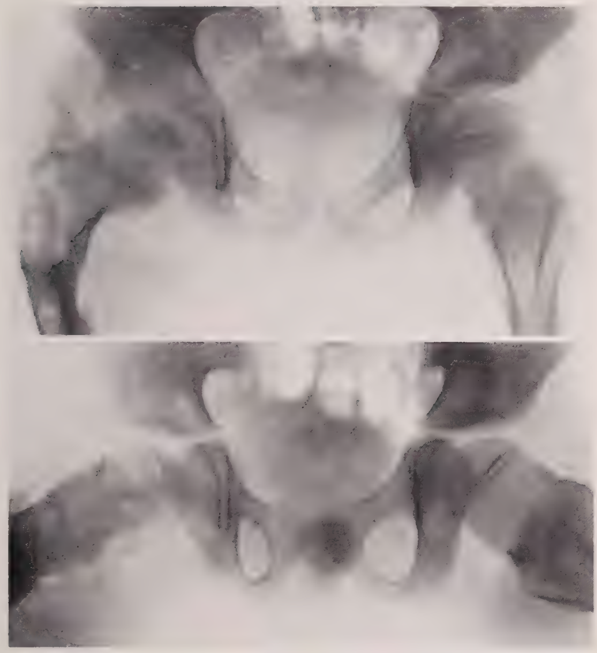

FIG. 6. These films taken on 3/3/76 reveal the status of healing of the femoral epiphysis at time of screw and side plate removal.

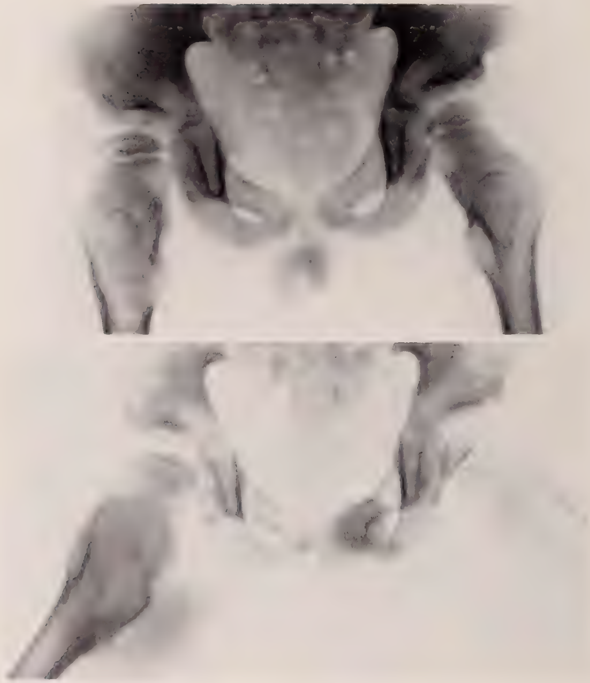

Fig. 7. Here are shown the early changes in the right hip of the second case in which Legg-Calve-Perthes disease coexisted with hereditary multiple exostoses. There is early fragmentation with much of the gross outline of the proximal femoral epiphysis retained.

and in the other with the femur equally affected in comparison to the uninvolved side.

One child studied in detail appeared to follow the usual pattern of L-C-P reconstitution. It is suggested that the Legg-Calve-Perthes disease developed as an unrelated concomitant process independent in its course and healing from the underlying hereditary exostoses.

Acknowledgment

The author wishes to thank Dr. Alan Reich for permission to cite the second case seen in consultation.

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Treatment of Diffuse Malignant Mesothelioma: A Review

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Abstract

Epidemiologic studies have anticipated an increase in incidence of malignant mesothelioma in the next decades, largely due to the wide utilization of asbestos. A thorough literature survey has been made of therapeutic modalities presumably available. In the series reviewed the prognosis is usually poor, whatever the treatment. Surgery can relieve temporarily such distressing symptoms as pain or recurrent pleural effusion. Radiotherapy, by conventional or high dose procedures, has led to partial control in some series, but not in others. Many different chemotherapies have been applied in small series of patients. Presently, adriamycin seems to be the most promising single agent. Local therapies are of little value. Controlled therapeutic trials are needed for more precise information about the treatment of this neoplasm.

The incidence both of pleural and peritoneal diffuse malignant mesothelioma (MM) is increasing (1–3). Because of the long latency from exposure to onset of the disease, the neoplasms associated with current levels of utilization and exposure to asbestos will not be evident until the 1990s (1). In view of this gathering storm, it is prudent to survey the therapeutic modalities presently available. There is no satisfactory evidence of even a single cure of an MM in the literature. The absence of effective curative treatment had already been stated by Saccone and Coblenz in 1943 (4), and is still true (5). In addition, due to the lack of controlled clinical studies, the effect of various therapeutic modalities published in scattered reports concerning small series of patients is hard to evaluate. The purpose of this report is to summarize the natural history of diffuse malignant mesothelioma, and to review the results of surgery, radiotherapy, chemotherapy and local therapies, alone or in combination.

I. *Natural History*

A) *Prognosis and overall duration*:

1. *Pleural MM*. Statements in the literature vary considerably regarding life expectancy (6).

The average delay of symptoms to treatment is 4 months (7). In general, survival is estimated to be less than or equal to about one year (2–10). The main data available in the literature are summarized in Table I. It is difficult to determine the natural course of the disease, because in most reported cases various diagnostic and therapeutic measures had been taken which may have affected the course. These figures are grossly similar to those indicated in earlier reports. In 1920, DuBray and Rosson (11) stated that the average

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TABLE I

Overall Survival of Patients with Diffuse Malignant Mesothelioma of the Pleura (Including treated patients)

Authors/Year		# of Cases	Survival in months from onset of symptoms			% patients dead at one year
			Mean	Median	Range	
Dubray & Rosson (11)	1920		6–9			
Geschickter (13)	1936	25	>24			
Saccone & Coblenz (4)	1943	19*			3–24	84
Hochberg (42)	1951	43*			3–48	86
Godwin (25)	1957	9	14	7	1.5–66	
Poulsen & Sorensen (33)	1959	27	9.9(+)			
Caffrey & Lucido (8)	1961	5	6		2–10	100
Sleggs et al (68)	1961	28				61
Manguikian & Prior (6)	1963	5	12		3–24	60
Semb (26)	1963	10	16.8	13	2–48	40
Newhouse & Thompson (22)	1965	42	14.6	12	2–30	50
Reisner & Huzly (10)	1967	33	<12			
Ratzer et al (32)	1967					
Epithelial Type		15	21	19	11–58	
Fibrosarcomatous Type		15	19	13	3–82	
Porter & Cheek (38)	1968	7		7	2–96	86
Roberts (2)	1970	20			<15	85
Oels et al (17)	1971	28				78
Whitwell & Rawcliffe (15)	1971	36				47
Elmes (7)	1972	250*	12			
Borow et al (69)	1973	72**		15–16		only 1 survival >19 mos.
Lilis & Selikoff (20)	1974	48	12.5		1–31	

* Cumulative literature series.

** Including 21 patients with peritoneal mesothelioma.

(+) Standard Deviation ± 2.4 mos.

duration of the disease from the onset of symptoms to death was from 6 to 9 months. Similarly, Robertson (12), in 1924, estimated the survival to be a few weeks to a year, "a little longer in rare instance." Actually, it appears that few patients live longer than 12 months (2). Table I indicates that in eight of 11 series, the majority of patients died before 12 months.

In some reports, however, survival may reach several years in individual cases. For Geschickter (13) the average duration of symptoms was 2 years in 25 cases. Le Roux (14) found symptoms one year before the treatment in four of nine patients, two years before in 2 patients, and 6 years before in the remaining one. Whitwell (15) supports the concept that pleural MM is a slow-growing disease, with 33% survival at 2 years, 17% at three years and 8% at five years. However, most of his cases had been treated with surgery and/or chemotherapy. In Owen's 15 cases, two cases (histologically proven at autopsy) lived for 6 years (16). Oels et al (17) reported a patient who lived 6 years 7 months after the onset of symptoms. Merlier et al (18, 19) also have a patient who lived seven years after an exploratory thoracotomy. These isolated cases of prolonged survivals not obviously attributable to therapy make prognosis difficult in the individual patient (2). Moreover, it has been stated that the effusions may dry up spontaneously in the course of the illness (5), due to accretion and adherence of pleural surfaces.

2. *Peritoneal MM.* The same controversy arises for the duration of peritoneal

MM. Most of the cumulative series indicate an average survival of six months (7) to 9.5 months (20) (Table II) which is even shorter than for the pleural MM. For Moertel (3) although occasional long term survivals have been reported with pleural MM, the peritoneal variety follows a more virulent course and death has uniformly been reported to occur in less than 12 months after the diagnosis is established. However, Winslow and Taylor (21) found an average survival of 18 months with a range from one to 60 months for 13 patients, and Newhouse and Thompson (22) an average of 14.8 months for 21 patients. Here again, the impact of various therapeutic measures is not clearly analyzed.

B. *Explanation for poor prognosis*:

The reason for such a lethal outcome probably is best explained by the course of the disease. The onset is often insidious, and even in some cases discovered incidentally before any symptoms, radical surgery is not feasible (23). The tumor spreads over the serosal surfaces of the parietal and visceral pleura, the diaphragm, the mediastinum and the peritoneum, leading to the "frozen thorax." It also extends into the interlobar fissures and into the lung substance (6, 13, 24–27). In addition, lymphatic dissemination is common (6, 25), with involvement of the hilar lymph nodes. However, lymph node enlargement may be due to a benign reactive hyperplasia only, as in the three of four cases reported by Campbell (24). Hematogenous metastases also occur, but their frequency has been controversial. Contrary to some earlier reports (13) distant metastases are now reported with high frequency in some autopsy studies (6, 20, 26, 28)—up to 84% of the 25 cases with autopsy studied by Schlienger et al (29). Although they have been described in nearly all organs, including the contralateral lung, liver, skeleton, brain, thyroid, adrenals, kidneys, and spleen (26), they are rarely the main causes of death, which are more frequently secondary to local tumor extension, respiratory insufficiency, cardiac failure and pulmonary emboli (29).

II. *Results of Surgery*

There are no published series in which matched groups of patients have been subjected to a variety of treatments in a prospective study. The results

TABLE II

Overall Survival of Patients with Diffuse Malignant Mesothelioma of the Peritoneum (Including treated cases)

Authors/Year		# of Cases	Survival in months after onset of symptoms			% Patients dead at one year
			Mean	Median	Range	
Godwin (25)	1957	4	12	11	1–26	86
Winslow & Taylor (21)	1960	12*	18	11	1–60	58
Newhouse & Thompson (22)	1965	21	14.8	12	3–54	50
Elmes (7)	1972	45*	6			
Lilis & Selikoff (20)	1974	68	9.5		2–29	

* Cumulative literature series.

of the various surgical procedures are, therefore, hard to evaluate (5). To emphasize the bias of a retrospective analysis, Elmes (5) has shown that the mean survival of patients who had a needle biopsy only (11.4 months, eight cases) or an open biopsy only (10.8 months, 27 cases) is longer than the mean survival of patients who had thoracentesis only (8.4 months, 26 cases) which is almost certainly related to case selection. It seems simpler to analyze the effects of surgery according to its aim—palliative or "curative" (radical)—in patients with pleural mesothelioma.

A. *Palliative Surgery*:

This term includes thoracotomy with biopsy, partial resection and decortication. Even if these are palliative procedures, their interest is not negligible for several reasons:

1) *Diagnostic Interest*: A large open biopsy is often the only reliable diagnostic procedure (8, 25, 30, 31). Cytology of the pleural fluid is often nondiagnostic (26). Cancer cells were identified in 15 out of 20 patients by Ratzer et al (32) but the diagnosis of mesothelioma was not made. Similarly, cytologic examination of the fluid in patients with MM showed tumor cells in 14 out of 26 examinations done by Poulsen et al (33), but the nature of the tumor was not identified. In a study of 15 cases of MM, cytologic studies were diagnostic only in two cases (34).

Pleural needle biopsy is difficult due to the thickness of the parietal wall; it was inadequate in eight out of nine patients for Ratzer et al (32), as well as in 10 out of 11 patients for Delajartre et al (34), and in 27 out of 37 patients for Schlienger et al (29). Scalene lymph node biopsy may be positive in case of palpable supraclavicular lymph nodes, but often the exact classification of the neoplasm remains uncertain (32).

At thoracotomy, the gross aspect of the pleura is by itself characteristic (35, 36). Frozen sections are unreliable and confusion with metastatic adenocarcinoma is frequent (35, 36). The paraffin sections confirm the gross aspect, which is easily recognizable by a trained surgeon.

2) *Effect on Quality of Survival.* Palliative surgery improves the quality of survival in two ways (14). Firstly these palliative procedures limit the reaccumulation of pleural fluid (5, 37–39). Although pleural fluid is often the chief cause of symptoms in mesothelioma patients (38), the dyspnea is rarely relieved by simple tapping (4, 26). Removal of the tumor mass provides new surfaces that lead to pleurodesis with obliteration of the pleural space. Secondly palliative surgery can relieve pain. This has been reported after palliative decortication (37) and even sometimes after a simple exploratory thoracotomy (30).

3) *Effect on duration of survival.* For LeRoux (14), palliative resections can provide "space in which the tumor may pursue its growth for a longer period with less interference with vital structures." However, there is little, if any, evidence that the survival is prolonged (5, 10, 32). The mean survival was 10 months for 5 patients treated by decortication by Ratzer et al (32) and also for 22 patients reported by Hertzog (37) which is (apparently) not better than the

results of exploratory thoracotomy only. However, palliative surgery seems more rewarding in MM than in bronchogenic carcinoma (30). It should be emphasized that no controlled studies are available, and that some long survivals have been reported which may be spontaneous.

B. *"Curative" or Radical Surgery.*

This term designates the cases where the entire tumor was apparently removed at surgery. These procedures include total pleurectomies and radical pleuropneumonectomies. They are rarely performed, as shown in Table III. The frequent involvement of the chest wall, the diaphragm and/or the lung necessitate extensive and difficult surgery. Some surgeons favor this aggressive approach (24, 26, 34, 35, 40). The majority find that survival is not prolonged, however, and that patients still die early from local recurrence (13, 14, 18, 19, 28, 31, 32, 37).

We were able to collect from various sources (Table III) 28 cases treated by radical surgery with accompanying survival data. There were eight postoperative deaths (28.5%). The known survival for 14 deceased cases ranges from 2 months to 55 months with a mean of 12 months. For 11 cases of pleuropneumonectomies (Table III) there were 4 postoperative deaths and the reported survivals for the 7 remaining patients are: 5, 6, 6, 7, 7, 9 and 26 months. These results are certainly not encouraging and have been recently confirmed by Butchart et al in a more homogeneous study of 29 personal cases (41). These authors performed a pleuropneumonectomy in all their patients, including in most cases an excision of the involved ipsilateral pericardium and diaphragm. Operative mortality was 31%. Median survival was four months for 11 patients with mixed epithelial and mesenchymal type, and 16 months for nine patients with epithelial type. The overall median survival was 8½ months for 20 patients. These authors therefore recommend this type of surgery for patients with epithelial mesothelioma. This opinion is not shared by Wanebo et al (40), who recommend surgery for fibrosarcomatous mesothelioma.

TABLE III

Surgical Procedures in Patients with Diffuse Mesothelioma of the Pleura

Authors/Year		Total # of Cases Operated	Palliative Surgery		Radical Surgery	
			Exploratory Thoracotomy (+ Biopsy)	Partial Excision or Decortication	Pleurectomy	Pleuropneumonectomy
Poulsen & Sorensen (33)	1959	19	2	13	4	
Caffrey & Lucido (8)	1961	5	3	1	1(+ lobectomy)	0
Merlier et al (18, 19)	1964–8	46	34	11	0	1
Ratzer et al (32)	1967	27	16	4	5	2
Hertzog & Toty (37)	1968	31	3	22	0	6
Porter & Cheek (38)	1968	7	3	2	0	2*
Delajartre et al (34)	1973	31	17	7	6	1
Total number of Cases		166	78	60	16	12
% of Total		100%	47%	36%	10%	7%

* Pneumonectomy without total pleurectomy.

Curative surgery has no place in the treatment of abdominal mesothelioma but omentectomy has been advocated as a reasonable palliative procedure.

III. *Radiotherapy*

Here again most of the reports give too few details to assess the efficacy of radiotherapy.

A. *Pleural MM*

1. *Conventional radiotherapy*: Opinions concerning conventional radiotherapy are contradictory. Some authors deny any benefits from it, although they rarely indicate its characteristics and report no controls (10, 13, 19, 26). Elmes (5) even states that palliative radiotherapy was avoided because it seemed "to cause the tumor to grow more rapidly through the chest wall and to involve the skin." Others have an intermediate opinion (28, 42), and for Saconne and Coblenz, radiotherapy "may give some temporary relief" (4). Ehrenhaft et al, using 2000 rads to 2500 rads in 4 patients, have observed a good palliation in 2 and no effect in the 2 others (36). Ratzer et al (32), out of 11 patients treated with radiotherapy, with tumor doses ranging from 1200 to 5000 rads, have observed one survival of 82 months. This patient had partial excision of the tumor, immediate postoperative radiotherapy to the residua and subsequent irradiation to areas with metastasis. Porter and Cheek (38) published a case treated with radiotherapy after biopsy, with a survival of eight years. The lack of controlled studies and the possibility of some isolated long survivals do not allow any firm conclusion.

2. *High doses and high-energy radiotherapy*: This method was described by Schlienger et al (29) and Eschwege et al (43). These authors use a 23 MeV betatron, giving a total of 3,500 rads to 7,500 rads by 3 sessions of 330 rads each per week, with a mean of 4,500 rads for 14 patients. Two portals were used, anterior and posterior, including the whole hemichest, ⅔ of the adjacent mediastinum, the diaphragm and the axillary and supraclavicular areas (43). The initial results seem encouraging when compared to another series of 24 patients treated by the same authors using palliative radiotherapy with a total of 1,000 to 3,000 rads (29, 43) (Table IV). The patients were not randomized, however, and comparison of the studies is not as valid as it would have been otherwise. For instance, the mean duration between the onset of symptoms

TABLE IV

Effects of "Palliative" and "Curative" Radiotherapy (RT) on Patients with Diffuse Malignant Mesothelioma of the Pleura in a Non-Randomized Study. (Adapted from Schlienger-Eschwege, et al (29))

	# of Cases	Mean Survival After 1st Symptom	Mean Duration 1st Symptom to Treatment	Mean Survival After Treatment
		(mos)	(mos)	(mos)
Palliative Rt	24	17.4	7.6	9.8
Curative Rt	8	25	12	13

and the beginning of the treatment seems shorter for the palliative group. The survival measured from the first symptom for 10 deceased patients treated by "curative" radiotherapy ranged from 11 to 52 months with a median of 27 months and a mean of 26 months (29, 43). The mean survival after the beginning of the treatment is only 13 months, however, as compared to 9.8 months for the palliative group (Table IV). In addition the two patients with the longest survivals from onset of treatment (26 months and 37 months) had also received chemotherapy with 5-fluorouracil after "curative" radiotherapy.

Objective responses noted included: relief of pain (but persistence of dyspnea), regression of vascular compression if any, and tumor necrosis at autopsy (2 cases). The tolerance to radiation was reported to be good with no side effects on skin, lungs or heart (43). The treatment, however, is long (4 to 5 weeks) and according to the authors, carries some risk to the spinal cord and to the heart. For these authors (29, 43) the risk of radiation pneumonitis is real, but without clinical significance since the patients are already dyspneic, and since the atelectatic lung is encased by the tumor and is practically nonfunctional. This precludes usefulness in bilateral disease. Voss et al (44) are more pessimistic about high-dose radiotherapy. These authors have treated 14 cases of advanced pleural MM with telecobalt or 42-MeV betatron, delivering about 4,000 to 6,000 rads to the hemichest including the mediastinum. They achieved a remarkable effect on chest pain, which disappeared completely in 10 patients. The survival, however, was short: 12 patients survived between four and 24 months, with a mean of 10 months.

3. *Peritoneal MM.* There is no general evidence that RT is effective in peritoneal MM (3). Lyle and King (45) observed no effect in 1 case by using 4,500 rads to the abdomen via two portals. In a case reported by Pendergrass and Edeiken (46), the tumor was reduced in size by 2500 rads, but reactivation of growth took place within a few months, leading to supplementary treatments until a total dose of 9650 rads was given over a period of four years. Temporary effects have also been reported by Winslow and Taylor (21). Here again, no definite conclusion is possible. Better results are reported for combined therapy of peritoneal MM in section VI.

IV. *Chemotherapy*

A) *Previous Results*

Isolated cases of MM have been reported which were treated with chemotherapy. No general conclusion is yet possible, due to the paucity of cases, the lack of information on the doses and schedules of chemotherapy, and the lack of controlled studies. Wolcott et al (47) have treated two patients with pleural MM, with a combination of nitrogen mustard 0.1 mg/kg i.v. daily and ACTH (60 mg intramuscularly 4 times a day) during 5 days, every 6 to 8 weeks. One case was a failure, the other showed some "definite palliation" after the first and second course but none later. Nitrogen mustard has caused no appreciable benefit for others (8, 28, 32). Cyclophosphamide has given some palliation (10): five years survival after exploratory thoracotomy in one case (37), decrease in pleural thickening during seven months in one case, and reduction of pain during three months in another case (30). Other authors found no appreciable effect, however (28, 32, 48). Gerner and Moore (49) reported three patients treated with 5-fluorouracil. Although one of them was a complete failure, the two others underwent a complete response of 17 months and 18 months duration respectively. These patients received a loading course of 15 mg/kg intravenously for 5 days and then a weekly maintenance dose between 500 and 700 mg. Methyl glyoxal bis guanyl hydrazone produced a 50% regression of 2 months duration in one of these patients. In a total of 6 patients, the same authors observed no effect with thiotepa, DTIC, adriamycin and glucosamine. The other drugs used sporadically in some cases are: chlorambucil (38), actinomycin D, methotrexate (32), Thiotepa, TEM, vinblastine (28). Steroids seem to have no effect (18). However, none of these studies are conclusive since no details on the procedure and the patients are given.

McGowan et al (50) have treated two cases of peritoneal MM with oral melphalan 0.2 mg/kg daily for 5 days every 4 weeks. Both cases had a complete response of 9 months and 22 months respectively, after 5 and 4 courses of treatment.

Dr. S. Waxman (personal communication) has treated nine patients with metastatic mesothelioma (6 pleural, 3 peritoneal). He used a combination of 5-fluorouracil i.v. 300 mg/M^2 per day × 4 days, cyclophosphamide i.v. 150 mg/M^2 per day × 4 days, and vinblastine i.v. 7.5 mg/M^2 on days 1 and 8. This regimen was repeated every 4 weeks. Five out of nine patients experienced symptomatic improvement (3 peritoneal and 2 pleural mesothelioma). Among them, two patients with peritoneal mesothelioma had an objective response (decrease in palpable mass in one case, decrease of ascites in another). The mean survival from onset of chemotherapy was 6.2 months for the four nonresponders and 14 months for the five responders.

Kucuksu et al (51) treated six patients with adriamycin at a dose of 50 mg/m^2 every 3 weeks. Two patients had a complete response lasting 19 and 7 months respectively, and three others had a partial response lasting 2, 6 and 9 months respectively. The same authors treated five patients with a combination of cyclophosphamide, vincristine, 5-fluorouracil, and methotrexate. One had a complete response lasting 19 months, and two had partial responses lasting 3 and 7 months. The overall median survival from diagnosis was only 9 months.

Bonadonna et al (52) have treated eight patients with pleural MM using adriamycin alone, at a dose of 60–75 mg/m^2 in a single injection, or 20–25 mg/m^2 for 3 consecutive days, every 3 weeks. Two out of eight patients experienced a complete response, with a median duration of response of 15.5 months.

Adriamycin has also been used in combination with DTIC (dimethyl triazeno imidazole carboxamide) by Gottlieb et al with three partial responses in 7 patients (53). Median duration of response was only 3½ months. The same group observed a partial response in two out of four patients with a 4-drug combination including cyclophosphamide, adriamycin, DTIC and vincristine (54).

VP-16-213, a semi-synthetic product derived from podophyllotoxin, has been used orally by Falkson et al (55) in four patients with mesothelioma, at a dose of 200 mg/day for 5 days every 16 days. No tumor regression was seen, only one patient improved, 2 showed no change, and 1 was a complete failure.

In a Phase I study of 5-azacytidine initiated by the Southeastern Cancer Study Group (56), a response was seen in 2 out of 3 patients with mesothelioma. This drug deserves further trials.

B. *Personal Data*

So far, adriamycin seems to be the most promising single agent. Clinical and experimental data suggest in addition that it has a radiosensitizing effect (57–59). Therefore, we have treated 14 patients with recurrent or surgically incurable pleural MM with a combination of adriamycin and radiotherapy (60). Treatment includes first a course of adriamycin alone, 30 mg/m^2 I.V. daily during three consecutive days. Three weeks later, they received a combination of adriamycin (½ dose, i.e., 15 mg/m^2 I.V. × 3 days) together with radiotherapy to the hemichest, which was continued for a total of two weeks. The total dose delivered was 2,000 to 2,500 rads midplane by one anterior and one posterior field. Three weeks after the completion of radiotherapy, adriamycin was begun again at 30 mg/m^2 I.V. daily × 3 days, every 3 weeks, for a total cumulative dose less than 550 mg/m^2 or until progression of the disease. All patients had previous thoracotomy for diagnosis. There were 13 males, one female. Mean age was 56 (range 36–71). All had a positive history of asbestos exposure, with a median latent period (from onset of exposure to first symptom) of 35 years. One patient is presently in complete remission for the past 32 months. Two patients underwent an objective partial remission of 12 and 18 months respectively, and 4 others a subjective improvement with stabilization during 3 to 6 months. The other 7 patients showed no response. The overall median survival was 9 months + from first treatment, and 14 months + from diagnosis.

One patient developed radiation pneumonitis 4 months after radiotherapy, which gradually regressed. Reversible leukopenia was noted in seven patients (median nadir 1500/cu mm) and reversible thrombocytopenia in two patients (nadir 78,000/cu mm). All patients developed alopecia; none had cardiac toxicity, cutaneous reactions, or "recall" phenomenon.

After progression, four patients were treated with a combination of 5-fluorouracil I.V. (12 mg/kg/day) and diammine-dichloroplatinum I.V. (20 mg/m^2/day) for 5 days every 4 weeks. Preliminary studies suggested that this drug combination is possibly synergistic (61). None of our four patients responded to that combination.

V. *Local Therapies*

Several cases have received some form of local therapy. Gray and Yom (62) in one case have instilled a total of 20 mg of nitrogen mustard into the chest via a thoracostomy tube, in divided doses, during the first four postoperative days after a surgical biopsy. There was no evidence of recurrence of symptoms or of pleural effusions during the one year of follow-up reported.

Radioactive colloidal gold (^{198}Au) has been used in several instances. No beneficial effect has been reported in pleural MM (Godwin-one case (25), Reisner and Huzly-two cases (10)) except for a single case with a "dramatic clinical improvement" for three and a half years after 100 mc and 85 mc of ^{198}Au (63). Similarly in 2 cases of peritoneal mesothelioma, ascites has been controlled by peritoneal installation of ^{198}Au (18, 45). The maximal effect of penetration of the beta particle from ^{198}Au is 3.8 mm, however; and 50% of its energy is dissipated in the first half millimeter (45). Therefore, it is inefficient in large tumor nodules, and its only indication is a diffuse involvement with tumor nodules smaller than 1–2 mm (29).

Talc poudrage is a well-known procedure to treat recurrent malignant pleural effusions (64). However, talc poudrage seems of no benefit in patients already treated by a palliative decortication (65).

A more unconventional approach has been described by Esposito (66) using local therapy with RNA extracted from hog's liver. The experimental basis of this treatment was the fact that RNA extracted from normal tissues inhibits the growth of tumors (66). After complete aspiration of the pleural fluid, 10 patients were treated only with 1 Gm of RNA intrapleurally, daily for 15 consecutive days without any other therapy. Two cases relapsed but in 8 cases all the symptoms were said to have disappeared, these patients remaining well 11.5 months after treatment (66).

VI. *Combined Therapies*

Some cases have been treated by combined therapies. The results of combined radical surgery and radiotherapy for pleural MM are summarized in Table V. Although no firm conclusions can be drawn, there appear to be two modal behaviors—short, 2 to 9 months, and long, 18 to 48 months.

Martini et al (39) treated 14 patients with pleural MM by removal of the bulk of tumor by pleurectomy, supplemented by external radiation to the entire hemithorax, and systemic chemotherapy. Although the exact modalities are not detailed, the authors state that control of disease is obtained in addition to control of effusion. Seventy-nine percent of their patients were alive at one year, and the median survival after pleurectomy was 16 months.

For peritoneal MM, Rogoff et al (67) treated four cases with intraperitoneal instillation of 10 mc of ^{32}P followed by abdominal radiotherapy, 1,600 to 3,000 rads in 3 to 4 weeks through opposing anterior and posterior fields. An additional 1,600 to 2,500 rads were given to the pelvis in 2 to 3 weeks. Three of these cases then received some chemotherapy (cyclophosphamide orally or cyclophosphamide and vincristine), but the doses are not specified. Two of these patients survived more than 10 years, one survived 1.5 years, and the 4th was alive 2 years after treatment.

Combined radiotherapy and chemotherapy with procarbazine seemed the only treatment of value for G. Falkson (personal communication). Procarbazine

TABLE V

Combined Radical Surgery and Radiotherapy (RT) in Patients With Diffuse Malignant Mesothelioma of the Pleura

Authors/Year		# of Cases	Surgery	Radiotherapy*	Survival After Onset of Treatment in Mos.
Godwin (25)	1957	1	Pleurectomy	Post-op	48
		1	Pleuropneumonectomy	Post-op**	8
Ehrenhaft et al (36)	1960	1	Pleuropneumonectomy	Local Radioactive Colloidal Gold 125 mc	2
Caffrey & Lucido (8)	1961	1	Pleurectomy & Lobectomy	Post-op	9
Le Roux (14)	1962	1	Pleurectomy	Post-op	18
		1	Pleurectomy	Post-op**	36
		1	Pleuropneumonectomy	Post-op	48
Ratzer et al (32)	1967	1	Pleurectomy	Post-op**	23
		1	Pleurectomy	Post-op**	18
		1	Pleuropneumonectomy	Pre & Post-op	5
Porter & Cheek (38)	1968	1	Pneumonectomy	Post-op	9

* No information available on modalities.

** Followed by chemotherapy, without information on modalities.

is started first, and then telecobalt. None of nine patients treated with telecobalt alone improved, whereas 14 of 26 patients treated with procarbazine and telecobalt improved from one to 20 months. The median remission time was 6.5 months in the group with combined treatment, the median survival time for responders was 23.5 months, while the median survival time for nonresponders was 10 months (G. Falkson).

In one personal case of malignant peritoneal mesothelioma tumor, regression and valuable palliation were seen after combined radiotherapy and chemotherapy (J. F. Holland and M. Friedman, unpublished). This 27-year-old woman underwent a laparotomy in August, 1970. There were massive peritoneal invasion by tumor, tumor masses scattered on the visceral and parietal peritoneum, and on the surface of the liver. Biopsy showed a tubulo-papillary mesothelioma and 60 mg of Thiotepa were given intraperitoneally. The patient then received abdominal radiotherapy using a strip technique (1,000 rads per strip), from 1/5/70 to 3/27/70. Procarbazine was given intermittently from February to June, 1970, at a dose varying from 50 to 100 mg orally per day. The palpable tumor masses were softer but not smaller. A second course of radiotherapy was given as a split course over a period of 2 months, from September to October 1970. The total dose was 3,000 rads to the whole abdomen, via one anterior and one posterior portal, using a 2 MEV unit. The kidneys were shielded at 1,500 rads. The palpable masses were reduced ln size. In May and July, 1971, she received two courses of adriamycin I.V. (30 mg/m^2/day × 3 days) and bleomycin I.V. (20 mg/m^2/day × 4 days) followed in September by adriamycin only. Despite this treatment, there was some enlargement of the tumor. From October, 1971 to February, 1972, she received 3 courses of methyl-CCNU p.o. (100; 100 and 125 mg/m^2). There was stabilization of the tumor. Since then, the patient received no further therapy and is presently alive and well 6 years after beginning of therapy. The tumor masses, although still palpable, have then gradually decreased in size.

Conclusions

Many therapeutic approaches to malignant mesothelioma have not yet been fully assessed in a systematic way. There would appear to be value to palliative surgery, radiotherapy, and to a variety of chemotherapeutic agents. Better progress can be anticipated with a more cogent application of the resources available in a study format.

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Examination of PH and O_2 Tension in Tube and Pedicle Flaps as a Method for Measuring the Blood Circulation

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The optimal time for separation of a flap, between 2–4 weeks has been advised by Gillies (1) and Hoffmeister (2). Circulatory tests have been proposed to judge optimal separation time by these and others: Lewis (3), Douglas (4, 5), Lange (6), Hynes (7), Barron (8). Nevertheless, a pink, soft, and warm flap over three weeks old can sometimes necrotize without the surgeon's being able to save it. We looked for a safe, easy and simple bedside method which would ensure valid information for the prediction of flap viability.

An adequate blood supply is the major factor in the survival of a flap. Measurements of both the capillary oxygenation and tissue PH indicate adequately the maturity of the flap. This examination is performed before and after clamping the base of the flap.

The control for these measurements is the contralateral side.

Materials and Methods:

Case 1. A 33-year-old soldier suffered a gunshot wound to his right elbow involving bone and soft tissue defects. A cross thoracal flap was designed and delayed. The design of this flap was made by cutting the margins on 3 sides. Before the flap was transferred to the elbow from its bed there was a delay of 2 weeks. Once the flap was transferred to the elbow we took capillary blood samples of both PH and O_2 tension of the flap. The findings are as follows: the O_2 tension of the flap in the 3rd week was 52 mm Hg. In comparison of 71 mm Hg with the normal bilateral part; and 81 mm Hg of his finger tip at the same time. A week later the O_2 tension rose to 56 mm Hg; 2 weeks later (i.e., 5 weeks after transfer) the O_2 tension rose to 66 mm Hg. The flap was then separated and set in. The values took one week after separation to fall down to 60 mm Hg. The PH remained constant in all regions 7.41–7.42 (Figs. 1—3), (Table I).

Case 2. A 38-year-old male suffered an amputation of his left leg above the knee and a compound fracture with bone and soft tissue defects of his right leg following a road accident. A thoraco-abdominal flap was delayed and tubed. Six weeks later the flap was separated at its upper end and transferred to the patient's right wrist. Three weeks after the transfer we started clamping the inguinal end.

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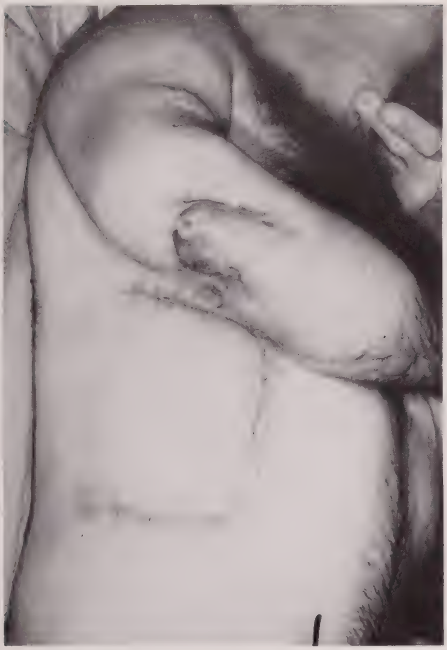

FIG. 1. Patient 1, the delayed flaps and the injured elbow.

TABLE I

O_2 Tension and PH of Case 1

	3rd Week		4th Week		5th Week		After separation	
	O_2 Tension	PH	O_2 Tension	PH	O_2 Tension	PH	O_2 Tension	PH
Flap	52	7.41	56	7.41	66	7.41	60	7.41
Healthy corresponding part of left side	71	7.41	70	7.41	72	7.41	71	7.41
Finger Tip	81	7.42	82	7.42	80	7.42	81	7.42

However, due to the mottled appearance of the flap, separation was delayed.

After 5 weeks the O_2 tension was 36 mm Hg at the wrist end of the tube (A), and 46 mm Hg at the base (B). We compared these measurements to a reading of 41 mm Hg at the wrist (C), and 61 mm Hg at his finger tip (D). The PH remained constant in all regions 7.40–7.42.

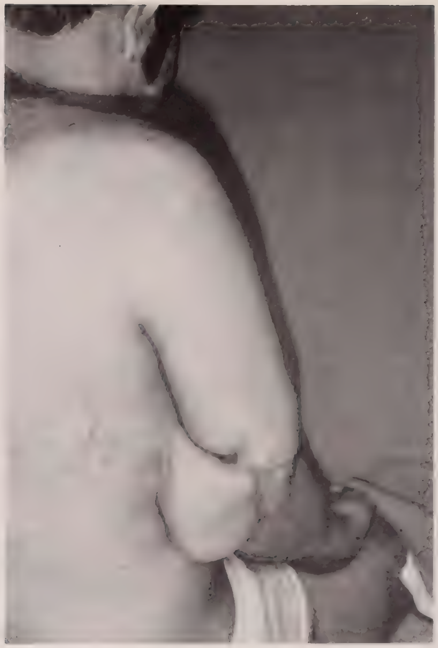

FIG. 2. Patient 1, the flap being crossed to the elbow.

TABLE II

O_2 Tension and PH of Case II

	5th Week				6th Week				8th Week			
	Before clamping		After clamping		Before clamping		After clamping		Before clamping		After clamping	
	O_2 Tension	PH	O_2 Tension	PH	O_2 Tension	PH	O_2 Tension	PH	O_2 Tension	PH	O_2 Tension	PH
Flap wrist end A	36	7.40	24	7.31	33	7.42	29	7.32	45	7.42	40	7.32
Flap inguinal end B	46	7.42	24	7.31	46	7.43	27	7.32	46	7.42	42	7.32
Forearms wrist C	41	7.42			41	7.42			41	7.42		
Finger Tip D	61	7.41			65	7.43			66	7.43		

After clamping the inguinal end for fifteen minutes the values of both the O_2 tension and the PH dropped. The tension to 24 mm Hg at both ends (A and B) and the PH to 7.31. One week later the O_2 tension of the flap was unchanged but after the clamping of the abdominal end the O_2 tension of the wrist end of the tube (A) rose to 29 mm Hg and the PH was 7.32.

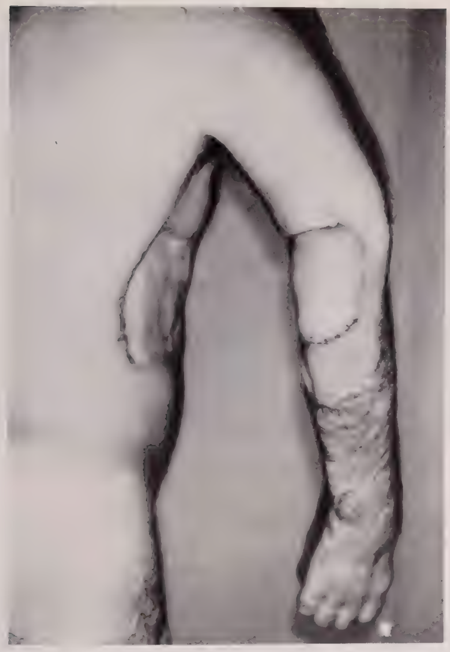

FIG. 3. Patient 1, the crossed elbow flap and the thoracal donor area covered with split thickness skin graft.

After 8 weeks the O_2 tension value was 45 mm Hg at the wrist end of the tube (A) and 46 mm Hg at the base (B). After clamping for 15 minutes the O_2 tension was 40 mm Hg at the wrist end of the tube (A) and 42 mm Hg at the base of the tube (B) (Figs. 4—6), (Table II).

Discussion

To determine if potent circulation has occurred within a tubed or pedicle flap it is necessary to occlude one end of it and observe whether or not adequate arterial and venous circulation has proceeded through the other end of the flap and maintained viability throughout.

The measurement of O_2 tension of a flap before and after clamping, can demonstrate if circulation of the flap is sufficient. This method enables one not only to rely exclusively on a clinical impression or on the accepted time of 2–4 weeks for separation of the flap.

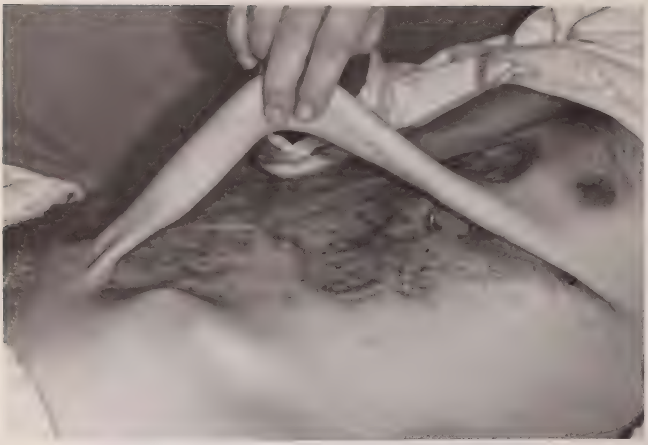

FIG 4. Patient 2, the delayed thoraco-abdominal tube flap.

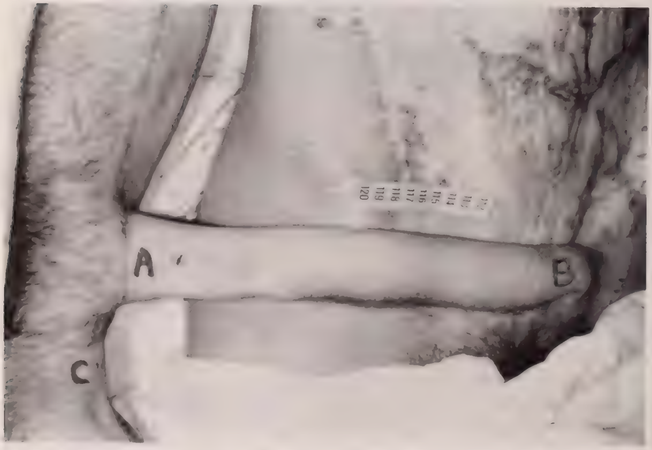

FIG 5. The thoraco-abdominal flap crossed to the right wrist. Its end (A) was deepithelialized and buried.

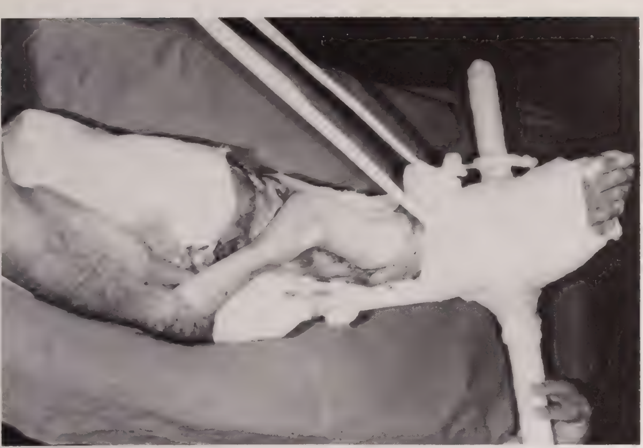

FIG. 6. The flap jumped to the right leg.

In our first case 5 weeks were necessary before a safe transfer of the flap could occur. In our second case we waited 8 weeks before the transfer was performed.

It must be noted that after clamping a flap at one end we arrived at different values of O_2 tension.

We presumed that clamping causes venous stasis to occur and a slight O_2 tension difference. We have concluded from the preceding experiments that 5 mm Hg O_2 tension is the maximal difference for successful separation.

The ultimate success of a flap transfer diminishes if at the time of transfer the O_2 tension difference between the flap and the contralateral normal side is greater than 5 mm Hg.

The sample for this primary experiment was limited. In order to provide scientifically exact results, further clinical experimentation is necessary and currently is being conducted.

Summary

A new bedside method, which ensures valid information, for the prediction of flap viability is presented. This method measures blood Ph and O_2 tension of the flap.

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Colposcopy in the Detection and Management of Patients with Cervical Intraepithelial Neoplasia

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Abstract

During an 18-month period, 141 new patients were seen in the Dysplasia Clinic at The Mount Sinai Medical Center for colposcopic evaluation of cervical disorders. No change was introduced in the management of these patients during this period, but based on the data acquired by colposcopic examination a new plan of management is suggested. With colposcopy it is possible to define the extent and location of epithelial change and to treat these changes with more limited techniques than surgical extirpation. An adequate colposcopic examination by experienced examiners is essential in the evaluation of the patient with an abnormal pap smear of any class. Repeat Pap smear proved to be of no value in short-term follow-up of cervical intraepithelial neoplasia.

Introduction

In the past 10 years the emergence of colposcopy in the United States has added a new dimension to the evaluation and management of patients with abnormal cervical Papanicolaou smears. Many reports in the literature (2, 3, 7, 11) have clearly shown the safety and reliability of colposcopy as a useful technique for locating the site of precancerous and invasive lesions detected by routine cytologic screening. In many centers the routine performance of cervical conization for diagnosis has been eliminated. Complete acceptance of colposcopy in the study of all patients with abnormal cytologic smears requires reeducation and change in the traditional philosophy of management. The purpose of this report is to review our management of patients with abnormal Pap tests at the Dysplasia Clinic at The Mount Sinai Medical Center since its introduction by the Gynecologic Oncology service in 1974.

Materials and Methods

During the period from December 1974 to July 1976 a total of 141 new patients were evaluated with colposcopy and directed biopsies. These patients were referred to the Dysplasia Clinic primarily because of abnormal cervical cytology ranging from mild dysplasia (class II) to carcinoma in situ or possible invasive carcinoma (class IV-V). Other referrals included patients who were being followed for previously treated cervical intraepithelial neoplasia, patients with inutero exposure to diethylstilbestrol and patients with gross cervical lesions. Several patients were seen on a referral basis from private attendings or from family planning clinics in the community.

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In all these patients cytologic smears were repeated, and a complete colposcopic examination was carried out. Most patients were evaluated by several examiners. This included inspection of the endocervical canal with an endospeculum, examination of the cervical portio, inspection of the vaginal fornices, and observation of the entire vaginal canal when indicated. The cervix and vagina were then swabbed with a cotton applicator soaked in 3% acetic acid to remove mucus. The cervix and vagina were viewed systematically with white light and subsequently with a green filter. Suspicious lesions were identified, and an accurate diagram was recorded in the patient's chart. The abnormal findings were selectively documented with several colpophotographs. Biopsies were obtained from the most abnormal areas, using Eppendorfer and Kevorkian forceps. If the entire transformation zone could not be fully visualized an endocervical curettage was performed. Hemostasis at the site of biopsy was usually obtained by simple pressure. Occasionally, application of Monsul's solution was required. All cytologic and histologic specimens were processed by the department of Pathology and a single pathologist interpreted all specimens. For the purpose of this preliminary experience the classification of cervical pathology was made by grading cervical intraepithelial neoplasia according to the definitions of Richart (10), Stafl (11), Kolstad (8) and others. Cervical intraepithelial neoplasia (CIN) grade 1 is mild dysplasia; grade 2 is moderate to severe dysplasia; and grade 3 is severe dysplasia to carcinoma in situ.

Diagnostic cervical conization was performed in all patients with histologic evidence of grade 3 cervical intraepithelial neoplasia or worse, in patients with unsatisfactory colposcopic examinations whose smears indicated grade 3 cervical intraepithelial neoplasia or worse, and when the histology of the biopsy was not consistent with the severity of the Papanicolaou smear. Cryosurgery using the freeze-thaw-refreeze technique (15), was performed in all parous patients with histologic evidence of grade 1 and 2 cervical intraepithelial neoplasia. There have been no significant complications following colposcopic biopsies and cryosurgery. No patient has required treatment for inflammatory disease or bleeding, and no medication was administered routinely.

Results

Of the 141 patients evaluated, 114 were younger than 35 years of age (Table I).

Forty of the 141 patients were nulligravidas, the parity of the other patients is shown in Table II.

TABLE I

Age

Age	No. of patients
16–25	43
26–35	71
36–45	16
46–55	5
>56	6

Our colposcopy usually followed the original pap smear performed elsewhere by one to four weeks. The repeat Pap smear at the time of colposcopy often differed from the previous original report (Table III).

Of 55 patients referred because of a class III Pap smear, 18 patients had class I when the smear was repeated at the time of colposcopy. Thirty-two had a class II pap smear and only 5 patients continued to have a class III Pap smear (Table IV).

Of 88 patients who were referred because of a class II or III Pap smear, the histologic diagnosis of the colposcopic biopsy revealed grade 2 or grade 3 cervical intraepithelial neoplasia in 53 and microinvasive carcinoma in 1 patient (Table V).

In 52 of 70 patients with class II or III Pap smears at time of colposcopy significant cervical intraepithelial neoplasia was found histologically on colposcopic biopsy (Table VI).

TABLE II

Parity

Para	No. of patients
0	40
1	26
2	37
3	24
4	6
5	5
6	3
Total	141

TABLE III

Results of Original Pap Smears and Pap Smears Repeated at time of Colposcopy

Class	Original pap smear	Repeat pap smear
I	11	58
II	69	73
III	55	8
IV	6	2
Total	141	141

TABLE IV

Comparison of Original Pap Smear and Pap Smear at time of Colposcopy 1–4 Weeks Later (141 Patients)

Cytology	Original pap smear	Pap smear at time of colposcopy (1–4 weeks later)				No. of patients
		Class I	Class II	Class III	Class IV	
Class I	11	8	2	0	1	11
Class II	69	31	36	2	0	69
Class III	55	18	32	5	0	55
Class IV	6	1	3	1	1	6
Total	141	58	73	8	2	141

Of the 117 patients with abnormal colposcopic findings, cervical intraepithelial neoplasia grade 2 and 3 was found on directed biopsy in 67, or 57% (Table VII).

There was complete agreement between the histology of the colposcopic biopsy and the cone biopsy in 25 of 35 patients. The histologic diagnosis of the cone specimen was more serious than that of the colposcopic biopsy in 1 patient of 141 (Table VIII).

TABLE V

Comparison of Original Pap Smear and Histology on Directed Colposcopic Biopsy (101 Patients)

Cytology	Histology on colposcopic biopsy			No. of patients
	No significant changes	CIN* (grades 2 & 3)	Microinvasive carcinoma	
Class I	6	2	0	8
Class II	20	24	0	44
Class III	14	29	1	44
Class IV	1	4	0	5
Total				101

* Cervical intraepithelial neoplasia.

TABLE VI

Comparison of Pap Smear Obtained at time of Colposcopy and Histology on Directed Colposcopic Biopsy (101 Patients)

Cytology	Histology on colposcopic biopsy			No. of patients
	No significant changes	CIN* (grades 2 & 3)	Microinvasive carcinomas	
Class I	17	12	0	29
Class II	14	49	0	63
Class III	3	3	1	7
Class IV	0	2	0	2
Total				101

* Cervical intraepithelial neoplasia.

TABLE VII

Comparison of Colposcopic Diagnosis and Histology on Directed Biopsy (117 Patients)

Colposcopic diagnosis	Histology of colposcopic biopsy		No. of patients	Percent
	No significant changes	CIN* (grades 2 & 3)		
White epithelium	23 (20%)	15 (13%)	38	33
Keratosis	6 (5%)	4 (3%)	10	8
Atypical vessels	4 (3%)	8 (7%)	12	10
Mosaic	8 (7%)	23 (20%)	31	27
Punctation	9 (8%)	17 (14%)	26	22
Total	50 (43%)	67 (57%)	117	100

* Cervical intraepithelial neoplasia.

TABLE VIII

Comparison of Histology on Colposcopic Biopsy and Surgical Specimen (35 Patients)

Colposcopic directed biopsy diagnosis	Conization diagnoses				No. of patients
	CIN* 1	CIN 2	CIN 3	Microinvasive carcinoma	
CIN 1					
CIN 2	3	10			13
CIN 3		6	15	1	22
Total					35

* Cervical intraepithelial neoplasia.

Discussion

Colposcopy serves a vital role in the assessment of patients with abnormal cytologic findings. It evaluates mainly the changes in vascular pattern of the cervix and it differentiates harmless non-neoplastic change from invasive lesions and cervical intraepithelial neoplasia (CIN), a term introduced by Richart (10) to designate the spectrum of intraepithelial disease as a continuum which antedates invasive cancer. A histologic diagnosis of CIN implies that the lesion has the potential of becoming invasive carcinoma and needs to be treated. The form of treatment-excisional biopsy, conization, cryosurgery or hysterectomy-depends on the extent of CIN, the patient's age and her requirement for future procreation.

We no longer consider conization mandatory if the lesion is entirely visible by colposcopic examination and there is no extension into the endocervical canal. This assumes that the colposcopist is experienced and that he is able to biopsy the most abnormal portion of the lesion. A high degree of accuracy can be achieved once experience is gained. No case of invasive carcinoma was missed in our experience.

There is no longer any place for delay in the evaluation of the patient with an abnormal pap smear of any class since we have seen 24 patients with grade 3 cervical intraepithelial neoplasia presenting with a class II pap smear.

It is particularly important to realize that if two cytology smears are obtained in rapid succession, i.e., a few weeks apart, the second smear may show substantially fewer abnormal cells than the first one. Thirty-one of 69 patients referred with a class II smear and 18 of 55 patients referred with a class III smear had negative pap smears at time of colposcopy 1–4 weeks later. Regardless of the reasons, any short-term follow-up study of CIN that claims disappearance of the lesions based on cytologic evaluation alone is dangerous. An abnormal pap smear of any degree requires colposcopic examination. The intelligent application of this technique can lead to accurate diagnosis with minimal penalty to the young patient requiring maintenance of her reproductive function or to the older patient in whom hospitalization and anesthesia are added risk factors.

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Bilateral Spontaneous Urinary Extravasation in Hodgkins Disease*

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Abstract

A patient with Hodgkins Disease treated by radiation developed bilateral parapelvic urinary extravasation. The mechanism of extravasation in this and other forms of chronic obstruction is postulated.

Spontaneous urinary extravasation is a well-described entity, usually noted during acute ureteral obstruction, most commonly secondary to calculus disease. The mechanism is generally felt to be secondary to a sudden increase in intrapelvic pressure (2), causing rupture of calyceal fornices and penetration of the fornix by urine (3).

Kaufman states that extravasation is secondary to pyelolymphatic backflow (4). Hinman, in his paper, includes three categories of physiologic forniceal backflow: 1) pyelolymphatic backflow; 2) pyelovenous backflow; and 3) at the most extreme end of this spectrum, pyelosinus backflow (Table I) causing peripelvic extravasation (5).

It is believed that chronic obstruction generally does not cause extravasation—that the slow development of the obstruction permits compensation by the kidney and collecting system to accommodate this increased volume load and to avert calyceal rupture (6). Nevertheless there have been isolated reports in the literature of chronic obstruction producing urinary extravasation. Recent articles describe this entity as occurring in association with retroperitoneal fibrosis (7), ureteral (8) and bladder tumor (9), benign cyst (10), prostatic carcinoma and metastatic breast carcinoma with retroperitoneal nodes (11).

Presented in this report is a case of Hodgkins adenopathy treated by radiotherapy presenting with bilateral urinary extravasation.

Case Report

F.Z. is a 36-year-old white woman, eight years postdiagnosis of Hodgkins Disease on cervical lymph node biopsy. At laparotomy for surgical staging three years prior to this admission, the patient was noted to have positive paraortic lymph nodes. She received a full course of radiotherapy to the abdomen and pelvis, in addition to multiple subsequent courses of radiotherapy and chemotherapy for local recurrence.

On 8/17 the patient was admitted to Mount Sinai Hospital with left lower quadrant pain and signs of peritoneal irritation on physical examination. IVP revealed left peripelvic extravasation. No calculi were visualized (Fig. 1). Retrograde study revealed multiple filling defects along the

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* Read at 74th Annual Meeting of the New York Section of the AUA, Nov. 12, 1976, Jerusalem, Israel.

TABLE I

Schema of Urinary Backflow after Ureteral Obstruction

Ureteral obstruction produces increased intrapelvic pressure, causing backflow:
1). Pyelo-tubular backflow (filling of tubules)—Reabsorption
2). Fornical backflow (penetration of fornix)
  a) Pyelolymphatic backflow—Absorption by lymphatics
  b) Pyelovenous backflow—Rupture into veins
  c) Pyelosinous backflow (dissection in sinus renalis, *peripelvic extravasation*)—Absorption by lymphatics

(Modified from Frank Hinman, Jr., *J. Urol.* 85-385, 1961).

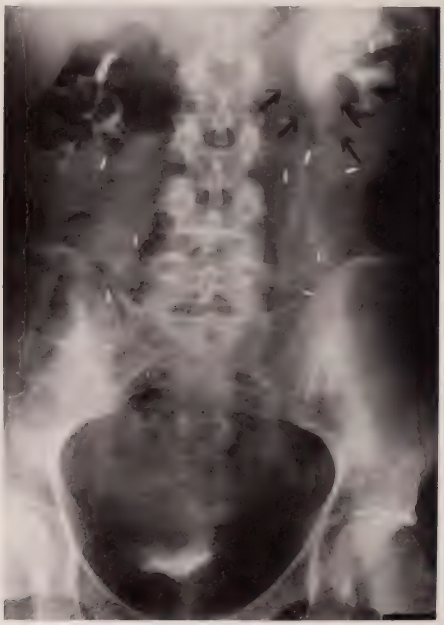

FIG. 1. IVP demonstrating left peripelvic extravasation.

course of the ureter, consistent with extrinsic compression by paraaortic lymph nodes (Fig. 2). Left ureteral catheterization was performed and the patient's symptoms subsided. Local radiotherapy was given to the involved nodes in the pariaortic area.

On 11/75 the patient was readmitted with right lower quadrant pain. Intravenous pyelogram revealed right peripelvic extravasation (Fig. 3). A ureteral catheter was passed to the right renal pelvis and left indwelling. The patient again became asymptomatic, and again received a course of radiotherapy to the periaortic nodes and pelvis. No stones or gravel were passed.

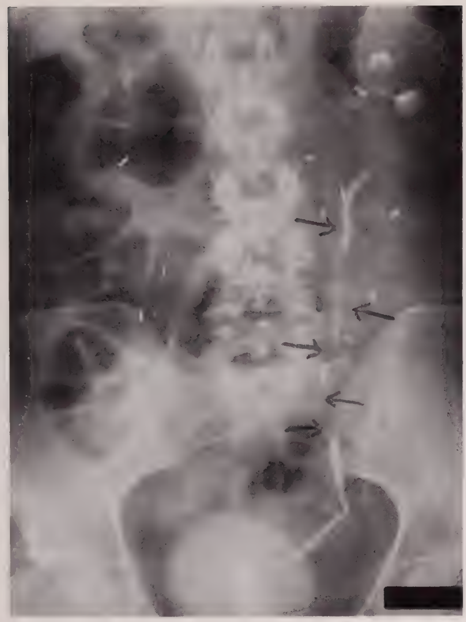

FIG. 2. Left ureteral retrograde showing multiple filling defects along the course of the ureter.

Discussion

This patient represents a form of bilateral spontaneous urinary extravasation in association with chronic ureteral obstruction by Hodgkins retroperitoneal adenopathy, complicated by previous radiotherapy.

The association of acute ureteral obstruction with urinary extravasation is understandable. The pelvis and ureter do not have the ability to rapidly distend and thereby accommodate the continued load of urine and increased intralumenal pressure generated by the acute obstruction. The result is rupture of the collecting system at the point of least resistance, usually the fornix.

The circumstances are different in chronic obstruction. The pelvis and ureter have ample opportunity for gradual distention, resulting in hydroureter and hydronephrosis, and in the process maintaining a relatively normal intrapelvic pressure, thereby averting extravasation. If such a collecting were, however, previously treated by radiotherapy, causing relative fixation of the ureter and renal pelvis—a form of iatrogenic retroperitoneal fibrosis—compensatory dilatation would then be inhibited and extravasation would then be more likely

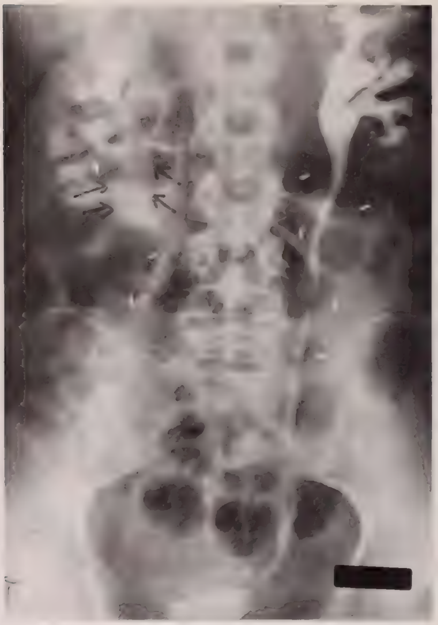

FIG. 3. IVP demonstrating right peripelvic extravasation.

to occur. Other anatomic derangements of the collecting system might similarly limit its distensability, and again lead to urinary extravasation.

With the increased longevity of patients with lymphomatous disease, and the increased use of radiotherapy in treating these patients, it is likely that the incidence of urinary extravasation will increase. The same background of paraaortic adenopathy and abdominal radiotherapy is also seen in testicular carcinoma, and it is entirely possible that extravasation may be encountered in this and similar situations.

Summary

Urinary extravasation from the calyces and renal pelvis is commonly found in acute ureteral obstruction, most often secondary to calculi. However, it can occur in chronic forms of obstruction provided that the ureter is prevented from distending to accommodate to the potential increase in intralumenal pressure. A case of Hodgkins Disease involving the ureter treated by radiotherapy is presented which illustrates this point.

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"Cryptic" Arteriovenous Malformation in the Pons: A Case Report

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The term "cryptic" vascular malformation was proposed in 1956 by Crawford and Russell (1) to designate small vascular malformations less than 3 cm in size.

McCormick and Nofzinger (12) found in the literature up to 1966, a total of 308 cases of cryptic vascular malformations of the central nervous system, and added 48 cases of their own. Eighty-five of 308 were located in the brain stem, mostly in the pons. As compared with large intraparenchymatous and/or dural vascular malformations, angiographically confirmed cryptic vascular malformations are extremely rare in the posterior fossa (12–14, 23). The purpose of this report is to present the angiogram of an exceptionally small arteriovenous malformation within the pons.

Case Report

A 36-year-old woman was admitted to the emergency room of the Nakadori Hospital on March 15, 1973. She suddenly complained of double vision, and numbness around the mouth, four hours before admission. These were followed by nausea and vomiting. Her history revealed that she had essential hypertension for several years.

On examination, the patient was alert and well-oriented. Blood pressure was 86/40 mmHg, pulse rate 74, respiration 28. Neurological findings were peripheral facial palsies, abducens palsies and vertical nystagmus on both sides. Other indications of the medial longitudinal fasciculus involvement were also noted. The fundi were normal; no stiff neck, Kernig or Brudzinski signs.

The spinal tap revealed clear, colorless CSF with an open pressure of 170 mm of water. No cells were found in the fluid. Spinal fluid protein was 16 mg per cent. Plain skull films showed no abnormalities. The electroencephalogram revealed border line records and the electromyogram showed bilateral peripheral facial palsies.

Angiographic findings (Fig. 1-3): Selective left vertebral angiography and angio-tomography were carried out via transfemoral catheter technique at the Akita Research Institute of Brain and Blood Vessels on the 25th hospital day.

In the arterial phase, there were several moderately dilated medial pontine arteries arising from the proximal portion of the basilar artery and a tortuous moderately dilated abnormal artery originating from the most distal portion of the left vertebral artery and supplying a small but definite vascular stain located in the midline lower pons. Dilated small tortuous veins were prematurely visualized in the arterial phase, draining into the retro-olivary veins (or lateral medullary veins), lateral pontine veins (8) and then into the petrosal vein. Neither arteries nor veins described above showed any deformities or displacements. The maximum size of the vascular stain was 8 x 7 x 4 mm. From the relationships of the posterior fossa structure portraied by the arterial and venous phases to Twining's and Swedish lines, the center of the lesion was indicated to locate within the lower pons (Fig. 4).

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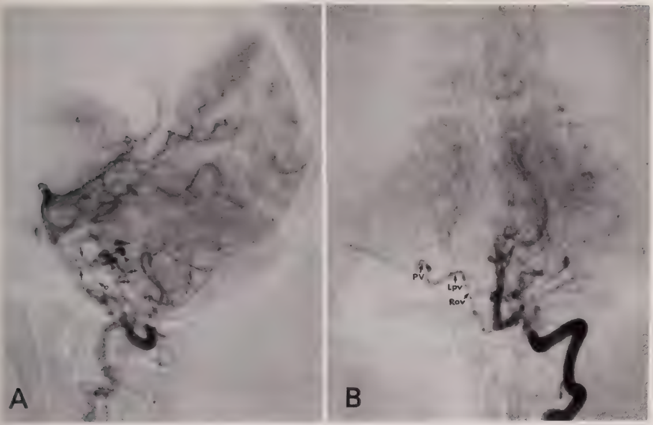

FIG. 1. Late arterial phase, vertebral angiograms; subtraction films. A) Lateral projection. Tortuous and moderately dilated draining veins are seen (↑). Vascular stain (two arrowheads) and feeding arteries (↑, ↑) are well visualized. B) Towne projection. The lesion is drained by large retro-olivary veins (Rov), lateral pontine veins (Lpv), and petrosal veins (PV).

No dilatation, diplacement or deformity of other posterior fossa vessels was noted. The angiotomograms performed on the same day confirmed the presence of the vascular stain, the arterial blood supply and the venous drainage. The patient improved and was discharged shortly after angiography. Follow-up examination three years later showed persistent left abducens and peripheral facial palsies.

Discussion

Based on different histologic principles (2, 11, 16, 18, 22), vascular malformations of the central nervous system have been classified into various types by neuropathologists and neurosurgeons. Arteriovenous malformations are considered to be congenital and are also known as arteriovenous aneurysm or angioma. They are rare in the posterior fossa. Krayenbühl and Yaşargil (9) collected 800 AVM from literature which were supplied by carotid and/or vertebral arteries. They reported that 85.7 percent of these were located supratentorially and 6.2 infratentorially. Reuter (15) also reported 6 cases of posterior fossa arteriovenous malformation in 247 angiographically-confirmed arteriovenous malformation of the central nervous system (12.5 percent).

Our case in this report showed a cryptic or an exceptionally small arteriovenous malformation measuring less than 1 cm in its maximum diameter. More accurate localization was confirmed from the relationships of the posterior fossa structure portraied by the arterial and venous phases of Twining's and Swedish lines.

The measurements indicate that the arteriovenous malformation was located in the medial dorsal part of the lower pons and the lesion, according to Verbiest

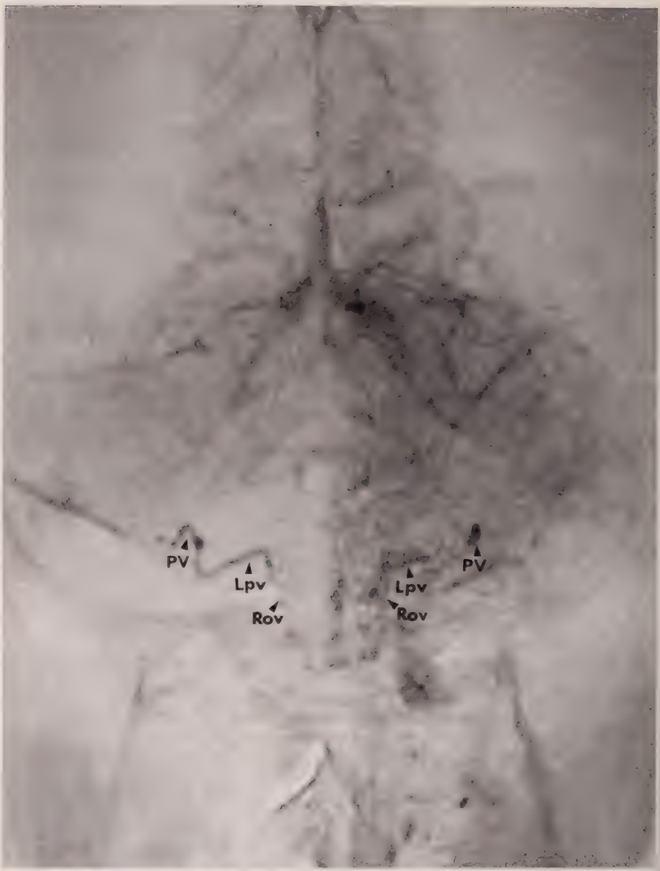

FIG. 2. Early venous phase, vertebral angiogram, Towne projection. The lateral margins of the medulla oblongata and the cerebello-ponto-medullary angles are outlined by retro-olivary veins (Rov), lateral pontine veins (Lpv) and petrosal veins (PV). The vascular stains have washed out.

(21), could be classified as an "intraparenchymatous" AVM of the pons. The affected region seems to coincide with the location of the medial longitudinal fasciculi, nuclei of abducens nerves and genua of facial nerves. Neurological findings were attributed to local bleeding or ischemia. The angiotomographic

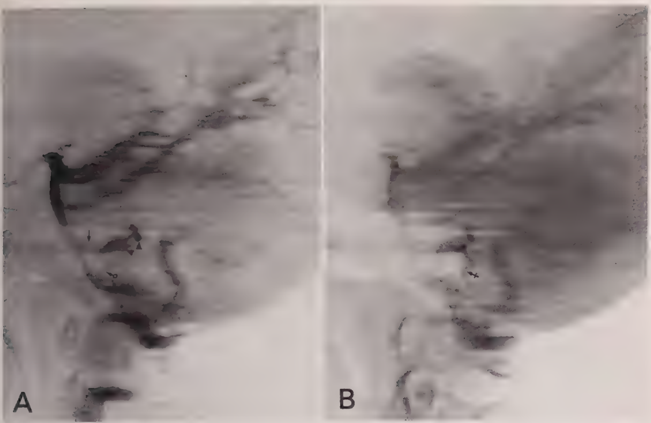

FIG. 3. Angiotomogram, lateral projection; subtraction films. A) Early arterial phase. Vascular stain (two arrowheads) and moderately dilated feeding arteries (↑, ↑) are seen. B) Late arterial phase. The dilated retro-olivary and lateral pontine veins (↑) are well seen.

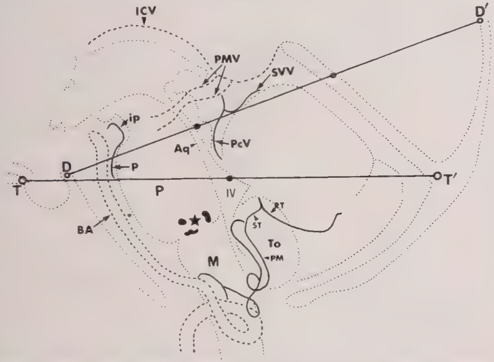

FIG. 4. Tracing and superimposition of the arterial and venous phases showing the relationship of the localization of the lesion to the posterior fossa structure. The midpoint of Twining's line (TT') is located in the fourth ventricle (IV), and the junction of the anterior and middle thirds of a line joining the tip of the dorsum sellae (D) through the midportion of the aqueduct (Aq) to the inner table of the cranial vault (D') (Swedish line) is very closely located in the posterior wall of midportion of the aqueduct. The relationships are indicative of the lesion (★) within lower pons. Other abbreviations are as follows: the posterior medullary segment (PM), supratonsillar segment (ST) and retro-tonsillar segment (RT) of the posterior inferior cerebellar artery, basilar artery (BA), interpeduncular segment (ip), and pontine segment (p) of the anterior ponto-mesencephalic vein, precentral cerebellar vein (PcV), superior vermian vein (SVV), posterior mesencephalic vein (PMV), internal cerebral vein (ICV), pons (p), medulla (M) and tonsil (To).

studies proved to be useful for more precise anatomical confirmation and localization of the lesion.

Summary

Angiograms of an exceptionally small arteriovenous malformation of the pons is presented.

Acknowledgment

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Parameters of in Vitro 21-Dehydroxylation of Deoxycorticosterone by Human Fecal Flora*

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Abstract

Acid formation from glucose in concentrations of 0.6% or more blocks 21-dehydroxylation of deoxycorticosterone in cultures of mixed fecal flora. This inhibitory effect may be offset, within limits, by proper buffering. 21-Dehydroxylating organisms, only observed in mixed fecal flora, appear to be weak competitors in cultures of fecal material. There is strong evidence that they form colonies on solid media. They may be preserved by lyophilization.

Introduction

21-Dehydroxylation of corticoids appears to be restricted to steroids undergoing enterohepatic circulation (1–4). Reductive dehydroxylation of steroids and bile acids has not been demonstrated in mammalian tissues. In contrast, organisms of mixed fecal flora of man (1) convert 11-deoxycorticosterone (DOC) to 3α-hydroxy-5β-pregnan-20-one (pregnanolone). The structures are shown in Fig. I. The conversion involves a reduction of DOC to tetrahydro-deoxycorticosterone (THDOC, 3α,21-dihydroxy-5β-pregnan-20-one) followed by a removal of the 21-OH group (5). Hydrogenation of Δ^4-3-CO is effectively done by *Clostridium paraputrificum* (5, 6), a member of the normal intestinal flora of man. Many non-sporing intestinal bacteria, and a few nonintestinal bacteria as well as 2 yeasts and 3 molds also perform the reduction, but in much lower yields (5–7). 21-Dehydroxylating organisms have not yet been obtained in pure cultures; however, some of their characteristics are predictable (1, 5). Additional characteristics of 21-dehydroxylating organisms are documented in this report with a view toward their eventual isolation in pure culture.

Materials and Methods

Media. Conventional bacteriological media were employed as previously described (1, 5). 21-Dehydroxylase activity was tested in a conversion medium (BHIC) of the following composition per L: dehydrated brain heart infusion broth (37 g) from Baltimore Biological Laboratories, Becton, Dickinson & Co.,

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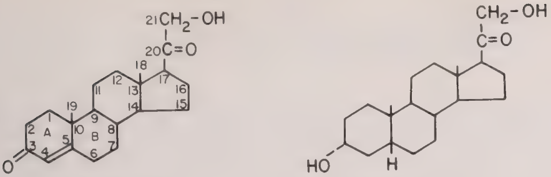
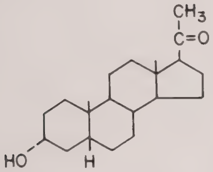


11-Deoxycorticosterone
(DOC)

Tetrahydro DOC
(THDOC)



Pregnanolone

Fig. 1. Structures of steroids.

Cockeysville, Md.; 0.5 g cysteine HCl; 1 g $NaHCO_3$; 4 ml 0.025% resazurin (J.T. Baker Chemical Co., Phillipsburg, N.J.) in water. The medium was distributed in 200 ml amounts in 500 ml Erlenmeyer flasks and autoclaved at 121C for 20 min.

Source and preparation of microorganisms. Fecal samples from healthy adults on the usual Western diet were collected in stool cups under ordinary atmospheric conditions. Processing began within 30 minutes of defecation (1). Serial ten-fold dilutions of the specimens were prepared in supplemented peptone broth (Becton, Dickinson & Co., Cockeysville, Md.). For convenience sake a 1000 fold dilution, for example, will be referred to as a 10^3 dilution or a 10^{-3} suspension.

Labeled steroids. 1,2-^{3}H DOC was purchased from New England Nuclear Corp. The steroid was at least 97% pure by isotopic dilution analysis. Prior to incubation the carrier was mixed with radioactive steroid to give 2×10^6 counts/min per culture regardless of the amount of carrier added to the medium.

Incubation. In conversion experiments cultures were incubated at 37C for 7 days (1).

Extraction of steroids, partition chromatography and *thin-layer chromatography* were carried out as previously described (1).

Determination of radioactivity. Tritium was determined by liquid scintillation counting (8).

Identification of steroids. Fractions comprising a peak of radioactivity eluted from a column were combined, purified if necessary, and identified by crystallization (1) or infrared spectroscopy (8).

Results

Effect of glucose on 21-dehydroxylation. Previously, we had observed that glucose in cultures of mixed fecal flora seemed to have an adverse effect on the conversion of DOC to pregnanolone. Accordingly, systematic investigations into the role of glucose in the conversion medium were performed. Table I shows that 1 ml 10^{-3} fecal suspension converted DOC (16 μg/ml) to pregnanolone, to metabolite X, tentatively identified as 20,21-dihydroxy-5-pregnan-3-one (5) and to small amounts of THDOC. The pH of BHIC prior to inoculation was 7.4 and at the end of the incubation 6.3. At a concentration of glucose of 0.6% or higher, pregnanolone was no longer formed, the cultures became increasingly acid, and DOC remained essentially unmetabolized. The inhibitory effect of 0.6% and 1% glucose on the 21-dehydroxylation could be offset by buffering the conversion medium with 0.15 M PO_4 (pH 7.2). This maintained the pH above 6.0. In the presence of 3% glucose the buffer failed to control the pH, and DOC was not metabolized.

Survival of 21-dehydroxylating organisms in sequential cultures of mixed flora. If the prevalence of 21-dehydroxylating organisms tends to increase in sequential cultures of mixed fecal flora, systematic subculturing would constitute an enrichment procedure, aiding the isolation of the organism. Flasks with 50 ml BHIC supplemented with DOC (16 μg/ml) were seeded with 0.25 ml 10^{-3} and 0.25 ml 10^{-6} fecal suspension, respectively. The cultures were incubated at 37C; at weekly intervals 0.25 ml was transfered to fresh BHIC with DOC, and the remainder was subjected to steroid analysis. Irrespective of inoculum size (10^{-3} or 10^{-6} suspension), 21-dehydroxylating capability persisted for at least five transfers, i.e., for a period of at least five weeks. Identical results were obtained when THDOC, rather than DOC, was the substrate.

The prevalence of 21-dehydroxylating organisms in the fifth sequential subculture of the mixed fecal flora was estimated by seeding 200 ml BHIC

TABLE I

Bacterial metabolism of DOC in BHIC supplemented with glucose

Media[a]	Glucose %	pH		Metabolites			Unmetab. DOC
		Initial	Final	Preg.	THDOC	X	
BHIC	0.2	7.4	6.3	+	Trace	+	–
	0.6	7.4	4.1	–	Trace	–	+
	1.0	7.4	4.7	–	–	–	+
	3.0	7.4	3.9	–	–	–	+
BHIC + 0.15 M PO_4 buffer	0.2	7.2	6.6	+	Trace	+	–
	0.6	7.2	6.4	+	–	+	–
	1.0	7.2	6.2	+	–	+	–
	3.0	7.2	4.6	–	–	–	+

[a] Inoculum 1.0 ml of a 10^{-3} fecal suspension.

[b] BHIC was rehydrated in 0.15 M phosphate buffer at pH 7.2.

containing DOC (16 μg/ml) with 1 ml aliquots of progressive 10-fold dilutions of this culture. 21-Dehydroxylation was achieved only with suspensions 10^{-1} and 10^{-2}. Addition of specific substrates to the propagation medium did not improve the results.

Evidence of colony formation by 21-dehydroxylating bacteria. The comparatively few 21-dehydroxylating organisms in feces suggest that isolation of these organisms will require the use of selective solid media perhaps combined with preliminary enrichment procedures (9). It was important therefore to ascertain whether or not the 21-dehydroxylating organisms form colonies on solid media. One ml aliquots of decimally diluted fecal flora were incubated with THDOC (16 μg/ml) in 200 ml BHIC. At the same time 0.1 ml 10^{-5} fecal suspension, the smallest amount of fecal material known with certainty to contain at least some 21-dehydroxylating bacteria (1) was spread on 5% sheep blood agar plates and incubated anaerobically at 37C for 2 days. The ensuing mixed growth was then harvested in 5 ml saline and decimally diluted. One-ml aliquots of the dilutions were incubated with THDOC (16 μg/ml) in 200 ml BHIC. As expected, 10^{-6} suspension of the fecal flora was the endpoint of 21-dehydroxylation (Table II). If 21-dehydroxylating organisms were unable to multiply on solid media, the harvested surface growth would at best produce pregnanolone when diluted 1:10 (equivalent to 10^{-7} fecal suspension). As it were, pregnanolone was formed from the surface growth diluted 10^4 (equivalent to 10^{-10} fecal suspension.

Tolerance to lyophilization. Cultures prepared from six months old lyophilized material of a 10^{-2} fecal suspension converted DOC to pregnanolone in yields of 60%–70%. Similar conversion rates were obtained with corresponding suspension of the original sample.

Discussion

In search of the unknown organisms synthesizing 21-dehydroxylase it is clearly necessary to monitor the pH of the medium. If glucose or any other

TABLE II

Multiplication of 21-Dehydroxylating Organisms on Solid Media

Dilutions	21-Dehydroxylation of THDOC[a] by	
	Fecal Suspension[b]	BAP culture[c] (Inoc = 0.1 ml 10^{-5} susp)
10^1	+	+
10^2	+	+
10^3	+	+
10^4	+	+
10^5	+	0
10^6	+	0
10^7	0	0

[a] 16 μg/ml in 200 ml BHIC.

[b] Inoculum: 1 ml.

[c] 0.1 ml 10^{-5} fecal suspension streaked on Blood Agar Plates and incubated anaerobically for 2 days; the ensuing growth was harvested in 5 ml saline and decimally diluted; 1 ml aliquots were inoculated into conversion medium.

fermentable carbohydrate is required for conversion, the medium should be buffered. A similar inhibitory effect of glucose on the in vitro 5β-reduction of cholesterol to coprostanol in cultures of human fecal flora was observed by Subbiah et al (10). It is less clear whether the acidity inhibits the 21-dehydroxylase or suppresses the growth of the bacteria synthesizing the enzyme. This distinction, however, is not important for the isolation of the organisms.

Isolation of 21-dehydroxylating organisms would be facilitated by the availability of an enrichment procedure. Sequential subcultures failed to accomplish this goal. Indeed, the 21-dehydroxylating activity of the bacterial suspensions decreased significantly between the first and the fifth subculture, indicating that under the described experimental conditions 21-dehydroxylating organisms are poor competitors in mixed fecal flora. Results of experiments in which DOC was added to the propagation medium tended to exclude the possibility of diminished production of an inducible enzyme. Regardless of the explanation, it is clear that sequential subcultures are of little help in attempts to isolate the 21-dehydroxylating organisms. At this point a search for selective inhibitors appeared unrewarding.

The experiments demonstrated that agar cultures of fecal suspension diluted close to the end point of 21-dehydroxylation, increased the 21-dehydroxylating activity about 10,000-fold. We interpret this as evidence of colony formation, an important concept since it provides a method of assessing the ratio of 21-dehydroxylating colonies to nonconverting colonies, which, in turn, could be utilized in attempts to isolate 21-dehydroxylating organisms.

Alternative explanations are possible. It could be argued, for example, that 21-dehydroxylating organisms did not grow on BAP, but that they require an essential metabolite, EM, manufactured by a hypothetical organism, M, which grows on BAP. In fecal dilutions EM is diluted out at 10^6-10^7, the limit of 21-dehydroxylating activity (1). Since culture M grows on BAP the harvested growth contains a new supply of the metabolite resulting in increased 21-dehydroxylation activity. Apart from lack of evidence for the existence of M, the hypothesis predicts that 10^4-10^5 dehydroxylating organisms should lay dormant on the blood agar plate during the anaerobic incubation. It follows that there would be a total of 10^{10}-10^{11} 21-dehydroxylating organisms per gm feces, or they would constitute more than 90% of the fecal flora. Under such circumstances 21-dehydroxylating organisms should have been detected in extensive attempts to demonstrate the enzyme among the more common fecal anaerobes (1, 5).

The fact that 21-dehydroxylating organisms tolerate lyophilization is of little interest to basic bacteriology. They could be preserved in liquid nitrogen. However, it is of considerable interest for future studies regarding the prevalence of these organisms in various populations with different diets and incidences of disorders of the colon.

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Evaluation of Human Placental Lactogen (HPL) Levels in Anencephaly

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Of the various hormonal and enzymatic tests that have been proposed for the assessment of fetal well-being, the determination of maternal estrogen levels in blood and/or urine and the placental hormone HPL have gained general acceptance (1, 2, 3, 4).

In anencephaly previous investigators have demonstrated that consistently low estrogen concentrations were a sign of the anomaly. However, a few cases have been reported in which urinary estrogen levels were in the low normal range (5). HPL concentration has been reported either as normal (6) or low (7).

Two cases of anencephaly are described in which low HPL levels were a major indicator of the abnormality.

Case Reports

(1) Patient F.D., a 24-year-old white para 0020, was first seen in the Prenatal Clinic on 6/26/73. Her LMP was on 3/10/73 after discontinuing oral contraceptives. She gave a history of two previous spontaneous abortions at 6 weeks each followed by D & C in Ecuador. When first examined the uterus was the size of 10 weeks gestation. Physical examination was otherwise negative. SMA-12, SMA-6, urinalysis and CBC were all within normal range, and Rh factor was positive. A sonogram at this time was compatible with 10 weeks pregnancy. Fetal heart was heard at 16 weeks. She was followed in the Prenatal Clinic. The uterine growth was below the normal curve throughout the pregnancy. Urinary estriols and HPL were determined and showed low values (graph); alpha-feto protein level was not elevated. At 36 weeks the sonogram was repeated showing no clear symmetrical outline of the fetal head. Fetal trunk was small and the extremities appeared larger than the trunk suggesting anencephaly or microcephaly. Flat plate of the abdomen confirmed the diagnosis of anencephaly. On 12/10/73, patient was admitted with ruptured membranes with cervix 4 cm dilated. After 3½ hours of labor, delivered NSD stillborn 1590 g—anencephalic. Placenta 260 g term meconium stained. Placenta surface appeared congested and hemorrhagic. No autopsy performed.

(2) A.W., a 22-year-old white hispanic, para 1021 was first seen on 1/28/76 in the Prenatal Clinic with unknown LMP. She gave a history of two previous elective abortions and one full-term normal spontaneous delivery. Physical examination revealed the uterus to be the size of a 28-week pregnancy. Fetal heart was audible and movements were noted.

SMA-12, SMA-6 and urinalysis were normal. Rh factor was positive. Sonogram for gestational age was suggested and refused by the patient at this time.

Sequential determination of blood and urinary estriols and HPL were made (graph). Alpha-feto protein determination was not performed because of late gestational age.

On the basis of low values of HPL and estriols and since no appreciable increase in uterine size was noted, patient finally consented to sonogram which was done at 31 weeks on 3/11/76. The results were not diagnostic of anencephaly and so a flat plate of the abdomen was performed

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establishing the said diagnosis. At 34 weeks on 3/29/76 after 10 hours of spontaneous labor, she delivered a 2600 g anencephalic that died shortly after birth. Placenta 300 g; no evidence of amnionodosum or other abnormality.

Postmortem examination showed grossly abnormal male fetus, with the following positive findings for anencephaly:

The combined weight of the adrenal glands were less than 1 gram (normal for 34 weeks is 7.1, ± 2.8). Thymus was larger than normal, 17 grams, (normal 8.3 ± 4.4).

The lungs were hypoplastic weighing 15 grams (normal for 34 weeks is 48 ± 14).

GUT—kidneys and ureters were absent, the penis hypoplastic.

CNS—the cranium shows the cavity above the tentorium to be very small and contained dura mater with small amount of red angiomatoid tissue. Pituitary, cerebellum, and brain stem were present.

Materials and Methods

Monitoring of the two cases started at a gestational age of 24 weeks for Case #1 and 28 weeks for Case #2. Estriols and HPL in blood and total urinary estrogens were serially determined.

Estriol levels were determined by a double antibody radioimmunoassay technique (Nuclear Medical Systems, CA). The normal range in the third trimester is from 5 to 20 nanograms/ml.

HPL concentrations were measured by radioimmunoassay (Pharmacia Diagnostics, N.J.). Values over 4 μg/ml after 30 weeks are accepted as normal.

Total urinary estrogens were determined by a modified Kober reaction (8). Concentrations below 10 mg/24 hrs were considered low for a third trimester.

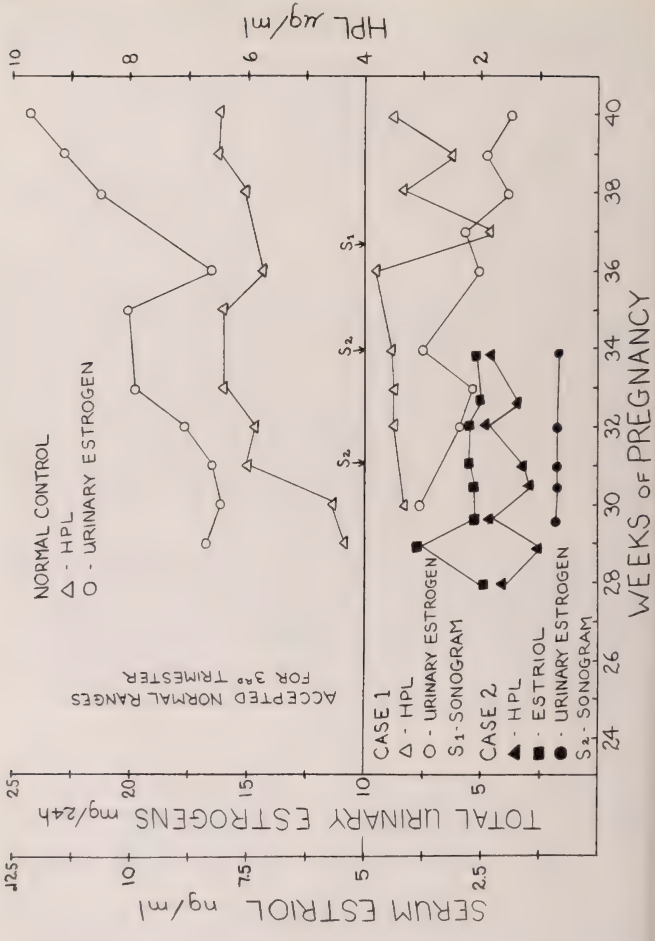
Results

As shown in the graph, in Case # 1 the results of HPL were below 4 μg/ml. Total urinary estrogens were below the normal for the gestational age. In Case # 2 very low levels of HPL obtained in serial quantitations presented a strong indication for a possible abnormal pregnancy. The subsequent determinations of total urinary estrogens were constantly at the 1 mg/24 h level, and paralleled the low concentrations of serum estriol. The sonogram was diagnostic only immediately before delivery.

Discussion

Anencephaly is one of the most common fetal gross anomalies. It occurs approximately once out of 450–500 births in the USA (9). The abnormality is caused by failure of development of the scalp, skull and brain. The endocrine system is highly affected causing abnormal hormonal production.

The concept of the feto-placental unit was suggested a decade ago (1). It tried to explain the mutual relationship of placenta and fetus in the synthesis of steroids, because certain enzymatic functions essential for steroidogenesis are present either in the fetus or in the placenta. Though all factors controlling the steroid synthesis are not known, it is supposed that in the fetal compartment the hypothalamic-pituitary axis must be involved. This is suggested by the fact that anencephalic monsters with different degrees of hypothalamic-pituitary defects secrete much less adrenal steroids than do normal infants. These steroids are secreted into the maternal circulation and can be quanti-


HPL µg/ml
10
8
6
4
2
NORMAL CONTROL
Δ - HPL
O - URINARY ESTROGEN
ACCEPTED NORMAL RANGES
FOR 3RD TRIMESTER
S₂
S₂
S₁
CASE 1
Δ - HPL
O - URINARY ESTROGEN
S₁ - SONOGRAM
CASE 2
▲ - HPL
■ - ESTRIOL
● - URINARY ESTROGEN
S₂ - SONOGRAM
24
26
28
30
32
34
36
38
40
WEEKS OF PREGNANCY
TOTAL URINARY ESTROGENS mg/24h
25
20
15
10
5
SERUM ESTRIOL ng/ml
12.5
10
7.5
5
2.5

tated in the mother's blood and/or urine. Laboratory tests based on estrogen concentration have been developed to ascertain the well-being of the fetus during pregnancy (6, 10, 11).

Josimovich and MacLaren (12) called attention to the hormone HPL (Human Placental Lactogen), produced by the syncytiotrophoblast (2) and found in the retro-placental blood. During pregnancy the concentration of this hormone increases constantly in the maternal circulation reaching the peak at 34–36 weeks of gestation (2). HPL has a very short half-life (20–30 min.) (5). Any change in production is quickly reflected in the maternal hormone content. Sudden decrease of this hormone was shown to be connected with problematic pregnancies (6, 11, 13). Despite some controversial data in the literature, the serial determination of HPL became an important index for monitoring the well being of the fetus, as related to placental function (2, 4, 14). Spellacy et al (15) consider values below 4 μg/ml in the third trimester as abnormal and introduced the concept of fetal dangerous zone (FD zone). HPL is said to reflect solely the placental function (10, 16, 17). The mechanism of HPL activity is unknown. Nevertheless, the role of this hormone as a regulatory mechanism of the feto-placental unit is suspected by exercising a metabolic effect on the maternal organism to provide the nutritional needs of the fetus (3, 15, 18). Only small amounts of HPL (between 5–10% of the maternal blood) are present in the fetal serum (5). However, in view of the short half life of the hormone and the demonstrations of constant low levels of HPL and estrogen in some anencephalic fetuses, we must raise the question whether these minute amounts of fetal HPL exert feto-placental activity. Since it is not known how the synthesis of HPL by the trophoblast is controlled, we may also ask, whether the hypothalamic-pituitary-adrenocortical axis may play a role in its regulation.

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Giant Synovial Cyst of the Shoulder and Perforation of the Nasal Septum in (a Patient with) Rheumatoid Arthritis

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Abstract

A patient with rheumatoid arthritis is described in whom two remarkable clinical observations were made; a giant synovial cyst of the shoulder and a perforation of the nasal septum.

Case Report

The patient is a 73-year-old white woman with rheumatoid arthritis of eight years duration. She has had recurrent admissions to Elmhurst City Hospital for severe exacerbations of her illness. Major manifestations of her rheumatoid disease have been deformities of the hands and knees, severe morning stiffness, limitation of motion and pain. The patient had been treated in the past with indomethacin, buffered aspirin and prophyxan. She had been confined to a wheelchair for two years prior to this admission. There was no other significant medical history.

On examination, the patient was pale and cachectic with normal vital signs. She had swelling of the right shoulder with several huge fluctuating masses overlying it and extending to the upper right arm (Fig. 1). Both shoulders were limited in mobility and tender. She had ulnar deviation of the wrists and deforming arthritis of the fingers and knees with clinically active synovitis. The examination of the nose revealed a small ($\frac{1}{2} \times \frac{1}{2}$ cm) perforation of the nasal septum.

The white count was 11,200/ml with a normal differential. Hemoglobin 10.2 grams %, erythrocyte sedimentation rate 87/mm/hour, latex fixation test 1:5100 and the anti-nuclear antibody test was negative.

The cyst of the right shoulder was estimated to contain 1.5 liters of fluid. When aspirated, the fluid was yellow, slightly turbid and formed a poor mucin clot. The white count was 19,000/ml with 65% polymorphnuclear cells. The gram stain and culture were negative. X-rays of the right shoulder demonstrated a destructive arthritis (Fig. 2). Arthrography was performed with a 19 gauge needle. Forty ml of fluid was aspirated and 12 ml of dye was instilled into the synovial sac. X-rays were taken and revealed a massive synovial cyst communicating with the subscapular and subdeltoid bursa (Fig. 3).

The patient was treated with systemic and intrasynovial installation of corticosteroids and her improvement was manifested by a reduction in the size of the cyst and increased motion of the shoulder.

Discussion

A huge synovial cyst of the shoulder and a perforation of the nasal septum are described in a patient with severe rheumatoid arthritis. Cystic distension of bursae and protrusion cysts arising from involved joints are added sources of discomfort and disability to the patient with rheumatoid arthritis. Such cysts develop as a result of fluid exudation into spaces lined by synovium and localized herniations of the synovial membrane through the overlying capsule.

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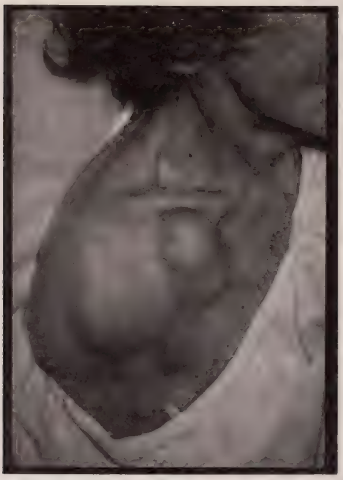

FIG. 1. Right shoulder. Several large fluctuating masses around the shoulder are seen extending into the arm.

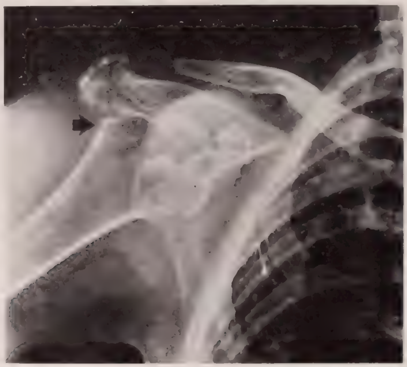

FIG. 2. Right Shoulder. Anteroposterior view reveals marked osteoporosis with joint space narrowing and subchondral as well as juxtaarticular cyst formation (arrow). Note clavicular resorption and tapering with resultant widening of the acromioclavicular joint.

Synovial cysts have been described in many joints (1)—the Baker's cyst of the knee being the most common.

In this patient arthrography was helpful in demonstrating the size of the cyst and the communications with the joint's bursae. The cyst was accompa-

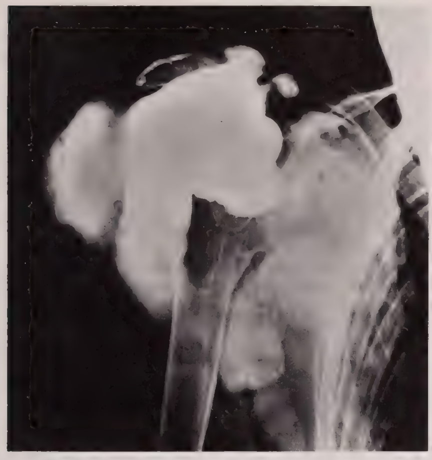

FIG. 3. Arthrogram. Instillation of contrast media into the cyst serves to delineate the massive synovial cavity and the abnormal communication with subacromial portion of the subdeltoid bursa. Note the filling of the huge subscapular extension of the synovial cavity and the numerous small nodular filling defects due to synovial hypertrophy.

nied by destructive arthritis and the fluid aspirated was highly inflammatory. Symptoms were pain and limitation of motion of a subacute nature and without sudden onset to suggest rupture of the cyst or rotator cuff tear (3). The patient was treated and improved with systemic steroids, repeated aspiration, local injections of steroids, rest and range of motion exercises.

Perforation of the nasal septum has been recognized in patients with systemic lupus erythematosus (4) and has recently been reported in four patients with rheumatoid arthritis as well as other rheumatic diseases (5). The pathophysiologic mechanisms leading to the perforation are unknown.

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Steroid Therapy in Myasthenia Gravis associated with Thymoma*

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Abstract

Thymoma has been encountered in 163 out of 1557 myasthenic patients observed. Myasthenia gravis (MG) in these cases is generally more brittle and difficult to treat with anticholinesterases alone. Although thymectomy is indicated for malignant potential alone, MG clinically improved as well, although less so than in the nonthymoma group. Where MG remained clinically unchanged postoperatively, steroid therapy was almost uniformly effective in producing clinical improvement or remission. This stands in marked contrast to the 30% improvement rate observed with steroids in Class IIB, III and IV patients without thymoma, who had not been thymectomized. This suggests that a different immunologic environment is more receptive to steroid control. These findings are also in harmony with our suggestion that MG develops through varying clinical and immunologic stages which require a progressive spectrum of therapeutic approaches. The vast majority of thymomas were of the lymphoepithelial type and germinal centers were frequently encountered in surrounding thymic tissue. Although not all thymoma-associated MG patients required steroid therapy for clinical control of myasthenic symptoms, a 100% improvement rate was noted when such therapy was used.

Introduction

During the past 25 years our group has observed and treated 1557 patients with myasthenia gravis (MG); 10.5% or 163 patients had thymoma. One hundred and twenty of these underwent surgery while 43 patients were treated with radiotherapy only. The clinical myasthenia associated with thymoma, whether benign or malignant, was more severe, brittle, and anticholinesterase control of symptoms was generally unsatisfactory. The addition of alternate-day corticosteroid therapy to our therapeutic regimen, initiated five years ago, has greatly altered the clinical behavior of thymomas associated with MG. The enhanced effectiveness of this treatment modality in this group of myasthenic patients as compared to 30% improvement with steroids or remission in Class III and IV myasthenic patients without thymoma suggests that we may be dealing with different pathophysiologic mechanisms. For this reason we reviewed the clinical, pathologic, and laboratory features of our entire population of patients with thymoma. The observations made here are in harmony with our previous suggestion that MG develops and progresses through varying

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clinical, immunologic and pathologic stages which may require different therapeutic approaches (1, 2).

Material and Methods

The clinical behavior of 35 myasthenic patients with thymoma while on alternate day Prednisone therapy was compared to that of 60 severe generalized myasthenics without thymoma receiving similar therapy. Thirty-two patients in the thymoma group underwent total thymectomy while three elderly patients were treated with radiotherapy alone. Thirty of the 60 patients in the non-thymoma group (ages 20–72), classified as IIB, III and IV, had undergone thymectomy. All tumors were of mixed lymphoepithelial or lymphocytic types. As pointed out previously, the incidence of thymoma was highest in the age group over 40 (2). The vast majority of these patients did *not* receive steroids preoperatively. Six patients referred to us from other institutions had received preoperative steroids without significant clinical response. Postthymectomy use of steroids was restricted to those patients who did not show significant clinical improvement within six months of surgery. Steroid therapy consisted of 25–100 mg Prednisone on alternate days. This modality was abandoned if no significant clinical improvement occurred after three months. Treatment was carried out either in incremental doses in the older age group, or by the immediate administration of a large dose of corticosteroids. Steroid therapy was tapered gradually after patients' symptoms had improved and clinical MG had stabilized. All patients have been observed for a minimum of two years.

Electrophysiological measurements were carried out in both groups pre- and postoperatively and again six months later. The technique has been described elsewhere (5). Responses were considered typical of MG if the amplitude of the second through sixth evoked potential showed a gradual decline and if the decrement of any of these potentials were greater than 10% when compared to the first. If no myasthenic deficit was elicited, a regional curare test was performed. Improvement was considered to be present if the postthymectomy decrement decreased at least 33% when compared to the prethymectomy decrement. Lymphocyte counts were also evaluated as a risk factor related to possible existing immune pathology.

We tabulated and examined the available clinical, pathologic and laboratory data of our population of 163 patients with myasthenia gravis and thymoma registered in the period 1951–1975. It should be noted that with changing indication for thymectomy we have operated on myasthenic patients earlier and some of these had thymomas which were not apparent on preoperative x-ray studies.

Results

Table I shows the clinical classification, sex distribution and number of thymectomies performed in 163 patients with MG and thymoma. It is readily apparent that thymoma is rare in ocular MG (Classification I) and most frequent in severe, generalized disease. Thirty-five of these thymoma patients with generalized MG were treated with massive alternate day steroids and/or

ACTH therapy and form the core of this study. Table II classifies the studied thymoma groups as to sex, age, clinical classification, operative findings and pathology. The average age of diagnosis of thymoma was 52.5 years and the cases were almost evenly divided among the sexes. Malignancy of tumor was assumed not only in cases of gross spread, but whenever the tumor capsule had been broken and adjacent tissues invaded. The presence of germinal centers in 16 out of 35 thymomas may be artificially low as in five cases the pathologist did not specify the presence or absence of germinal centers; and slides were not available for review. Furthermore, the diagnosis of thymoma in three instances was made by x-ray only and no surgery was performed.

Table III shows the average duration of MG prior to diagnosis of thymoma. It ranged from 1–10 years. Three patients who came to thymectomy were found to have benign, encapsulated thymomas despite having shown x-ray evidence of a mediastinal mass for 1–4 years previously. The data suggest that this type of tumor may be relatively slow growing. The simultaneous appearance of clinical MG with the diagnosis of thymoma was frequently associated

TABLE I

*Clinical Classification and Sex Distribution of 163 Patients with Myasthenia Gravis and Thymoma**

	Clinical classification						Sex				Totals	
	I	IIA	IIB	III	IV	All	Men		Women			
No thymectomy	3	8	15	17	8	51		18		33		51
Transthoracic thymectomy	5	18	31	36	4	94	70	44	93	50	163	94
Transcervical thymectomy	—	9	6	1	2	18		8		10		18
All	3	35	52	54	14							

* In 3 instances the diagnosis of MG was not made preoperatively. However these cases occurred during the early phases of investigation when clinical electromyography was not routinely performed preoperatively.

TABLE II

Patients with Myasthenia Gravis and Thymoma Treated with Steroids Post-Thymectomy

Number of patients	Sex		Average age (range)		Benign	Malignant*	Germinal centers	Clinical classification				
	Female	Male	Female	Male				I	IIA	IIB	III	IV
35	18	17	50.8 yrs (18–73)	47.6 yrs (29–65)	21**	14	16	0	6	9	13	6

* If tumor capsule was broken and tumor was adherent to/or had invaded adjacent structures.

** Three treated with radiotherapy and followed for three years or more without clinical evidence of spread.

TABLE III

Patients with Myasthenia Gravis and Thymoma Treated with Steroids Post-Thymectomy

Number of cases	Average duration of myasthenia gravis prior to diagnosis (range)	Alive	Dead	Survival time	Myasthenia gravis as cause of death
35	2.5 years (<1–10)	24	11	<1–15 years	0

with Class III behavior as previously noted (2). Similarly, the presence of occult thymoma suggested itself when MG occurred after age 40 or when preexisting, well regulated MG suddenly went out of control for no obvious reason.

Sixty-six percent of thymoma patients were alive at the time of this study yielding a survival time ranging from 1–15 years. A fair, average survival time, however, could not be calculated since 10 out of 35 patients had been under our care for less than three years. It is noteworthy that in the past seven years none of the deaths were caused by MG, but were due to tumor effect or unrelated causes.

Table IV summarizes the salient clinical, pathological and laboratory differences between MG with and without thymoma. Most startling is the difference in clinical improvement of MG in these two categories. Improvement was defined if a patient's clinical classification could be moved by at least one category and was maintained for at least six months. While clinical MG improved post-thymectomy in about 25% of patients with thymoma, improvement was markedly delayed compared to that of patients without thymic tumors. Alternate day corticosteroid therapy was effective in significantly ameliorating the myasthenic symptoms in 17% instances of thymoma-associated MG preoperatively while 30% of MG patients with severe generalized disease without thymoma responded significantly prior to thymectomy. Post-thymectomy, the entire thymoma group showed clinical improvement while only 50% of nonthymomatous patients did so. In the tumor group the clinical

TABLE IV

Effect of:	On myasthenia gravis alone	On myasthenia gravis with thymoma
Thymectomy	85% improved (391)	25% improved (112)*
Steroids	30% improved (19) Prethymectomy 50% improved (30) Post-thymectomy	17% improved (6) Prethymectomy 100% improved (35) Post-thymectomy
Anticholinesterase response	Variable (1553)	Brittle, poor, more frequent crises 70% (135)
EMG response after thymectomy	34–60% improved (60)	13% improved (35)
Presence of germinal centers in thymus	65% (391)	46% (35)
Humoral muscle antibodies (avg.)	40% (300)	94% (30)
Associated extrathymic neoplasms	1/147 patient/years of observation (126 in 1557)	1/39 patient/years of observation (17 in 163)
Elevated carcinoembryonic antigens >2.5 ng	10–42% (361)	33% (33)
Associated diseases of altered immunity	Increased 21% (1553)	Markedly increased 38% (163)

( ) Number of cases.

* Improvement markedly delayed. This figure refers to our experience with thymomas operated upon until 1972. Recent results in patients operated upon earlier in the course of the disease indicate better results.

improvement was always observed within four weeks of start of therapy and lasted for at least six months. Alternate day steroid therapy was abandoned if no significant clinical improvement became manifest after at least three months of 50–100 mg Prednisone on alternate days. Ten day courses of 100 units of ACTH gel daily were equally effective in eight patients. In many instances where patients were acutely ill and in respiratory crisis, treatment was begun with ACTH and improvement maintained by subsequent alternate corticosteroid regimen. However, it must be stated that while the positive response to ten-day courses of ACTH in the non-thymomatous myasthenic sample was more effective than alternate day steroid therapy, the ACTH induced improvement lasted only an average of 2½–3 months. Thymectomy potentiation of steroid therapy previously reported was again observed (2, 6).

Steroid therapy has to be employed because of the unpredictable and poor response to anticholinesterase therapy. The thymoma-associated MG was usually of the more severe clinical types IIB, III and IV, and respiratory crises were frequent. Ocular MG was only rarely associated with thymoma and in those rare instances probably indicated a thymoma of relatively short duration. Anticholinesterase response in our overall MG group depended on clinical severity and type of illness and was more successful in Groups I and IIA, less so in IIB and least in III and IV. In the nonthymomatous group, MG patients operated on within one year of onset of disease showed EMG improvement. However, if patients were followed for over a year (up to three years) the improvement rate rose to 80% (2, 5). Similarly, there was an inverse relationship between presence of germinal centers and improvement, i.e., the more germinal centers, the less early improvement (2). Age was not a real factor. These findings were in sharp contrast with a postthymectomy 13% EMG improvement rate noted in four out of 35 myasthenics with thymoma.

Germinal centers deserve special attention since their presence is an index of abnormal immune activity in the thymus (7, 8). Germinal centers were present in 65% of our thymectomized myasthenic population, being slightly more numerous in females (68% vs. 58%). The incidence of germinal centers rose with increments in duration and severity of MG. Thus, their presence appears to be a more reliable prognostic factor than the preoperative duration of MG symptoms which is often difficult to delineate accurately. In patients with MG onset after age 40, germinal centers were present in only 20% while the incidence was 46% in thymoma patients in this series. As a large percentage of these patients developed myasthenia gravis after the age of 40, the incidence of germinal centers is higher than in nonthymoma patients of the same group. Yet this incidence is still misleadingly low as it reflects the generally late onset of thymoma-associated myasthenia gravis (2). Benign thymoma were more frequently encountered if interval between diagnosis of MG and thymectomy was less than a year. Also noteworthy is the 46% incidence of thymoma in the group of myasthenics thymectomized above age 40. This would strongly tend to refute the published concept that no patient above age 45 should undergo thymectomy (9).

Another startling difference observed between the two groups was the higher incidence of circulating skeletal muscle antibodies. Using the immunofluorescent complement fixing technique previously reported by our laboratory, we found an overall incidence of 40% IgG antibodies in non-thymomatous myasthenics, ranging from 10% in the ocular classification up to 75% in some patients with severe generalized disease (10). Within each clinical category patients with thymoma had higher incidence of antibodies with greater titers as compared to myasthenics without thymoma. However, the incidence was 94% in thymomatous myasthenia and equally high in a small group of malignant thymomas without associated MG. Recent experiments with humoral antibodies to purified acetylcholine receptors have yielded similar results for MG alone (11–13). Table IV also summarized previously reported differences observed in the two groups as to oncogenic risk and associated autoimmune diseases (2, 14–17).

We have no statistics available to support a recent report that steroids in addition to thymectomy and radiotherapy significantly prolongs survival time of myasthenic patients with invasive malignant thymomas (18). However, isolated observations (three cases) in patients who had been reoperated for thymoma recurrence following radiotherapy showed that epithelial cells had not been affected by radiotherapy.

Comments

Previous reports have shown variable rates of MG improvement after corticosteroid therapy (19, 20). Our comparatively low improvement rate of 30% in the non-thymomatous myasthenic population reflects variation and duration of severity of MG. Furthermore we never employ steroids in the early phases of the illness.

The clinical observation that thymoma-associated MG responds better to steroids pre- and postthymectomy than severe generalized MG alone suggests either a different pathophysiological mechanism for thymoma-associated MG or a more malignant or advanced form of the disease. It is conceivable that a different immunological process may be operating at the synapse; and that this altered immunologic environment is more receptive to immunosuppression and steroid control. A high frequency of thymomas and autoantibodies has been reported in patients with HL-A_2 antigens while HL-A_8 antigen seems to be more prevalent in females with onset of MG prior to age 35 and in patients with thymic hyperplasia (21, 22, 23). Germinal centers, normally absent in the thymus, are the hallmark of antibody production (5). It is therefore not surprising that thymuses of myasthenic patients contain an abnormally large percentage of B-lymphocytes and gamma globulin (7, 8). In tissue cultures MG thymocytes, unlike normal human thymocytes, are known to synthesize significant amounts of immunoglobulins (8). It is not yet known whether these immunoglobulins represent antibodies to acetylcholine receptors, although soluble fractions of thymus do show immunologic cross-reaction with acetylcholine receptor proteins (24). Abramsky et al have shown that the reaction of MG lymphocytes to acetylcholine receptor protein is largely abolished when patients are treated with corticosteroids (25). What initiated thymus germinal center activity or thymitis is not clear. Our hypothesis in 1971 suggesting a viral invasion as the original inciter is still attractive, but remains unproven (26). Thymectomy and/or thymomectomy probably acts by abolishing or decreasing the life span of circulating sensitized lymphocytes and possibly also by abolishing the production of a thymic hormone which Goldstein feels may be a synaptically detrimental substance (27). Recent work has demonstrated that existence of at least three different antibodies to receptor protein at the postsynapse in MG patients (13). It is conceivable that certain of these antibodies are present in greater amounts in thymoma-associated MG and are more susceptible to steroid suppression. Yet several patients who had received steroids preoperatively were found to have thymoma at time of thymectomy. It is not clear whether this represents coincidence or cause-effect relationship. All thymomas, whether benign or malignant, probably represent late or advanced stages of thymic reactivity in which the earlier manifestations are hyperplasia and germinal center formation (28). This has been borne out by the previous report which shows the declining incidence of thymoma and Group IV patients since we have begun performing thymectomies in the very early stages of MG (2). The association between delay in thymectomy and invasiveness of thymomas suggests subsequent transformation of previously benign tumors. This, compared with lack of reliability of x-ray diagnosis, argues for early thymectomy, preferably by the transcervical route (15). It has been our practice to perform thymectomy via sternotomy in those instances where x-rays showed a large and/or low lying mediastinal mass. However, where x-ray indicated a small lesion located high and immediately behind the sternum, we have been able to remove the thymoma via the transcervical route in eight out of eight cases. In one instance a small manubrial window was created. Figure 1 summarizes our concept of the relationship of MG to the development of thymoma and autoimmune disease. While not all patients with thymoma-associated MG required postthymectomy steroid therapy, this treatment modality became necessary in the majority of these patients. There was no absolute correlation between the ability to control symptoms with anticholinesterases and thymic pathology. While patients whose thymomas had broken through the capsule and spread to adjacent structures had more severe clinical MG, clinical symptoms still responded to steroids. The concomitant administration of 10cc gamma globulin intramuscularly every three weeks increased the clinical efficiency of steroid therapy and allowed for earlier reduction in the administered alternate day Prednisone dosage (29). The same observation was also made in patients with MG not associated with thymoma. To date five patients whose steroid therapy was discontinued after 12–18 months of therapy have experienced recurrence of severe clinical MG symptoms after marked improvement or complete remission, but again responded promptly to reinstitution of alternate day steroid therapy. This suggests the prolonged existence of autoimmune activity at the postsynapse after thymectomy and thymomectomy. For this reason we have decided to keep all patients with thymoma-associated MG on small doses of Prednisone (5–10 mg) on alternate days indefinitely. Myasthenic patients with thymoma who died, died

FIGURE 1

NATURAL COURSE OF MYASTHENIA GRAVIS

PATHOLOGY	Normal	Start of MG (cause?)				Autoimmune Changes ? Thymitis ? Ab fixation to ACH receptors		Irreversible Changes (Atrophy of motor end plates)
CLINICAL CLASSIFICATION:	Normal	(X)	I	IIA	IIB	III	IV	Burnt out MG
						Brittle MG (Crises, thymoma)		Resistant to most therapy
RESPONSE TO:								
Anticholinesterase (0 - 4+)	--		4+	3+	2+	1+ - 0		0
Steroids			Not indicated		4 - 3+	4+ - 0		0
Thymectomy				3 - 4+ Ideal time for thymectomy		2+ - 0		

PRE-THYMIC PHASE

1. Absence of germinal centers in thymus.
2. Normal lymphocyte, T-cell, CEA data.
3. Few thymomas (non-malignant).
4. Earliest post-thymectomy remission.
5. Fewer extrathymic neoplasms.
6. Most marked post-op EMG improvement
7. Most frequent spontaneous remissions.

THYMIC PHASE

1. Increasing severity of disease.
2. Lymphocyte, T-cell and CEA abnormalities.
3. Increased extrathymic neoplasia.
4. More malignant thymomas.
5. More delayed response to thymectomy.
6. Increased incidence of germinal centers.
7. Less improvement in post-op EMG findings.

LATE THYMIC PHASE

as a result of tumor effect or associated diseases, but not from MG. We have no data to support a previous report indicating that steroids may suppress tumor growth regardless of histology and prolong life (18). We have employed radiotherapy selectively to shrink large tumor masses which were primarily composed of lymphocytes. In our experience we have not observed epithelial cell thymoma shrinkage after steroid or x-ray therapy.

While not all thymoma-associated MG patients required steroids for control of clinical symptoms, we did observe a 100% improvement rate among those who did.

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A Method for Gallbladder Bile Collection without the Need of a Thomas Cannula

J. M. SOTO, M.D., A. E. WALLEN, AND D. A. DREILING, M.D.

Experimental methods for the quantitative in vivo collection of uncontaminated bile from dogs usually employs a permanent duodenal fistula. The duodenal cannula of Thomas (1), through which either the common bile duct or the pancreatic duct is cannulated under direct vision, is the most satisfactory technique currently used when coupled with the Rudick adaptor (2).

Disadvantages of the Thomas cannula technique are many:

1) Animals must be kept under direct close observation.
2) Seepage and loss of bile around the glass cannula may occur before cannulation can be carried out.
3) Unphysiologic placement of a permanent fistula in the anterior duodenal wall, i.e., fixation of duodenum to anterior abdominal wall, loss of normal motility.
4) Collection of bile in the cannula well when the animal is in its normal position.
5) Accidental dislodgement of the Thomas cannula therein resulting in dehydration and death if repair is not carried out immediately.
6) Movement of the animal may dislodge or break the glass tube adaptor, the glass cannula, or cause injury to the common bile duct.
7) Occasional need of anesthetizing the dog in order to obtain samples, thereby changing physiologic parameters.

We have, therefore, utilized a highly resistant medical grade tube (Silastic ®) to overcome these difficulties and to facilitate a simplified method for short-term collection of pure gallbladder bile. A detailed description of this method follows.

Description

A Silastic®, sterile, medical grade Keofeed tube size 9.6 french is utilized with an external diameter of 3.18 mm and an internal diameter of 1.98 mm (Hedeco).

After capping the tube with a rubber infusion site seal, it is prepared by filling with heparinized saline solution. Carrying out a high midline incision, and visualizing the gallbladder, a purse-string suture #000 silk on a fine noncutting needle is placed at the gall-bladder fundus. The diameter of the purse string should be no more than 4–5 mm in size.

Therein a subcutaneous tunnel is constructed from the middle of the wound

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below or over the rib cage to the right posterior mid-scapula line lateral to the vertebral column. The infusion site seal is sutured to the skin by the use of 2 identification sutures *or* brought through the skin where it is anchored by a purse-string suture for easy identification and sample withdrawal. After determining the most appropriate length for the silastic tubing and allowing for visceral movements, 2 holes of approximately 1–2 mm in diameter are cut in opposite walls of the tubing. By the use of a #11 pointed blade a small hole is made in the gallbladder fundus within the purse string suture line. The silastic tube, previously marked with a stay suture 6–8 mm above the last tube opening is inserted by the use of a mosquito clamp. The purse string suture is tied and then anchored to the tubing marker as an anchoring suture.

Comments

Although the use of this method in our laboratory is recent, the ease with which specimen may be drawn has convinced us of its efficacy. Experiments on 5 dogs with the use of intraoperative cholecystokinin has indicated that the gallbladder remains physiologically intact, i.e., retains its storage capacity and its ability to contract. Intestinal continuity and integrity are not interrupted. Gallbladder bile is collected in its purest form. The system is ideal for sampling isotopic labeled bile acids in short-term studies (4–6 weeks). The collection technique can also be modified to allow for complete bile diversion or interruption of the enterohepatic circulation by shunting at the gallbladder level by ligating the common bile duct obviating many problems inherent in present protocols utilizing in vivo Erickson isotopic washout determinations (i.e., cystonephrostomy, vesicojejunocystic bypass).

Summary

A method for use in experimental animals requiring bile acid sampling is described. The technique obviates the need for implanting Thomas cannula and simplifies studies requiring quantitative as well as qualitative collection of bile.

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Ophthalmologic Notes

KEITH M. ZINN, M.D., EDITOR

Preoperative Management of Choroidal Detachments in Patients with Retinal Detachments

Submitted by

KEITH M. ZINN, M.D.

When a patient presents with a choroidal detachment(s) in the presence of a rhegmatogenous retinal detachment, in the same eye, careful evaluation of the choroidal mass(es) is in order prior to any surgical repair of the retinal detachment. It is a well known clinical observation that patients who have retinal detachments accompanied by choroidal detachments have a poorer visual prognosis than patients with comparable retinal detachments without choroidals. One of the most essential tests that can be used preoperatively to evaluate the choroidal masses and help in their management is A and B scan ultrasonography (Fig. 1.). The following case is presented to illustrate this point.

S. H. was a 61-year-old Caucasian male who presented in September, 1975 with decreased vision in the right eye of several weeks duration and was noted to have a retinal detachment with choroidal detachments in that eye.

Previous ocular history included open angle glaucoma (O.U.) for the past ten years which was treated with 1% Pilocarpine medication topically O.U. The patient had cataract surgery in the left eye (1974) which was followed by "uncontrollable glaucoma." Several cyclocryopexy procedures were performed (O.S.) to try and control the intraocular pressure, however, the patient sustained a retinal artery and vein occlusion in the left eye (1974) leading to total blindness O.S.

In 1974, glaucoma filtering surgery was performed on the right eye which appeared to control the intraocular pressure. The following year the patient had cataract surgery in the right eye. Approximately three months post-cataract surgery, the patient developed a retinal detachment with several choroidal detachments in that eye.

The patient also had a history of a "bleeding gastric ulcer." In 1973, there was a severe gastric hemorrhage which was almost "fatal." Through multiple blood transfusions and other medical modalities, the patient stabilized and has not had a recurrence of gastric bleeding up to the present time.

Ocular examination was as follows: Visual acuity, with correction, was HM-2 in the right eye with a +15.75 diopters sphere = −4.00 diopter cylinder axis 95° and no light perception in the left eye with a +13.25 diopter sphere = −1.25 diopter cylinder axis 80°.

Extraocular motility studies revealed an exotropia of 15 prism diopters. Otherwise there was a full range of motion of either globe in all standard fields of gaze.

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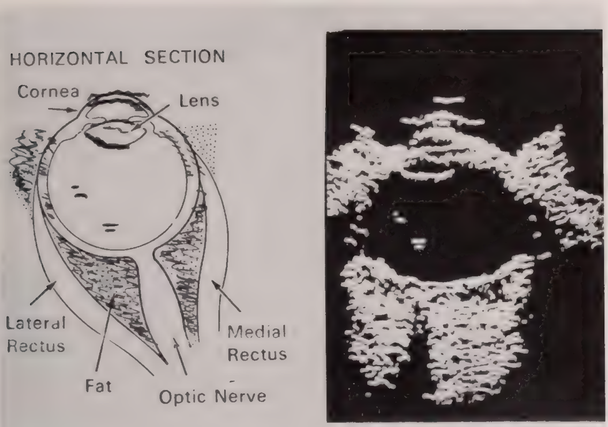


FIG. 1. B-scan ultrasonograph of a globe (horizontal section) in a normal adult. Left panel—schematic cross-section of the globe and orbit. Right panel—note the anterior and posterior surface echoes of the lens capsule. The vitreous cavity is acoustically quiet with an occasional artifact echo (small double lines). The retrobulbar fat pattern consists of a series of fine echoes with an inverted V-shaped region (without echoes) which represents the optic nerve shadow.

Cranial nerve function III, IV, V (ophthalmic division), VI and VII were grossly intact bilaterally. There was a marked depression of the visual field in the right eye and the patient was totally blind in the left eye.

The lids, ocular adnexae and lacrimal gland apparatus were within normal limits except for mild blepharochalasis O.U. The bulbar and palpebral conjunctivae were within normal limits bilaterally. Filtering blebs were present at the limbal zone in the 11:00 o'clock and 1:00 o'clock meridians O.D. The blebs contained subconjunctival (uveal) pigment. The corneae were clear and the sclerae were otherwise normal bilaterally.

The intraocular pressures were 15 mm. Hg. in the right eye and 70 mm. Hg. in the left eye by applanation tonometry. Slit lamp examination and gonioscopy of the anterior chambers revealed a sealed angle from the 1:00 o'clock meridian clockwise through the 11:00 o'clock meridian in the right eye. A superior sector iridectomy was present between the 11:00 and 1:00 o'clock meridians O.D. The left eye, on gonioscopy, had a sealed angle from the 1:00 o'clock meridian clockwise through the 12:00 o'clock meridian. A peripheral iridectomy was present between the 12:00 o'clock and 1:00 o'clock meridians. Neovascularization of the anterior chamber angle was present at the 10:00, 2:00 and 6:00 o'clock meridians O.S. Otherwise, the anterior chambers were of moderate depth centrally and the aqueous compartments were clear bilaterally. A benign looking iris nevus was present in the left eye. The irides were brown bilaterally. Pupillary reactions were poor in both eyes showing evidence of pupillary escape bilaterally.

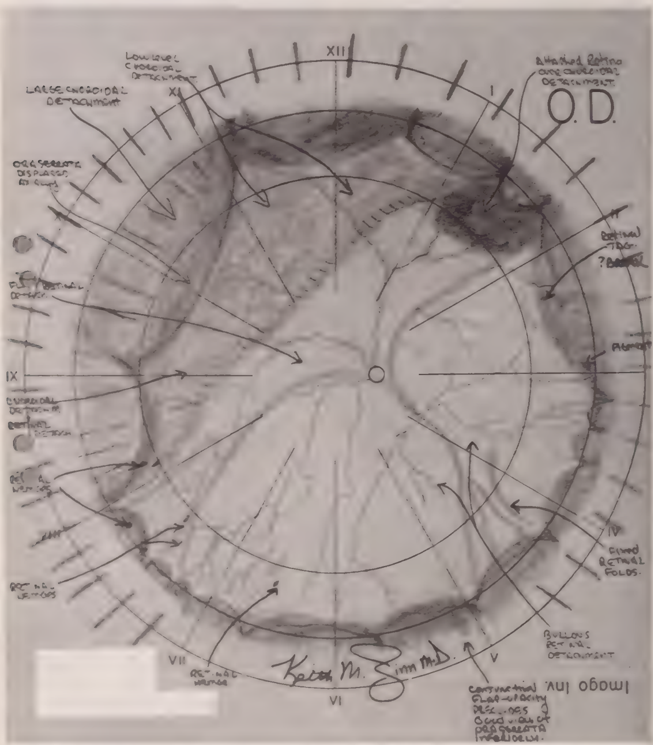
The patient was aphakic O.U. There were bilateral posterior cortical vitreous detachments. Trace to 1+ cells (pigmented) were seen in the right vitreous cavity, whereas the left vitreous cavity was clear.

Funduscopic examination revealed well demarcated optic nerve heads O.U. Glaucomatous cupping was present with optic pallor and a nasal shift of the disc vessels bilaterally. The cup/disc ratio, in the horizontal meridian, was 0.6 O.D. and 0.9 O.S. The vein/artery ratio, at the disc margins, was 3/1.0 O.U.

Indirect ophthalmoscopy revealed a retinal detachment with numerous choroidal detachments in the right eye and a possible retinal break at the 2:30 o'clock meridian (see Fig. 2). Indirect ophthalmoscopy on the left revealed some minor sheathing of retinal vessels, with extreme narrowing of the retinal arterioles. Also a vitreous "floater" or opacity was present overlying the optic nerve head and was part of a posterior cortical vitreous detachment O.S.

Clinical Course: Because of the history of a gastric bleed, it was elected not to give the patient a trial of systemic steroids in an effort to reduce the choroidal detachments preoperatively O.D. The choroidals looked unremarkable and a B-scan was not done preoperatively. At the time of surgery, attempts to drain the choroidals were unsuccessful. A white, cheesey material was present in the suprachoroidal space which contained masses of lymphocytes and plasma cells (see Fig. 3). This picture was consistent with a diagnosis of reactive lymphoid hyperplasia of the uveal tract.

Postoperatively the patient had A & B scan ultrasonography confirming the solid nature of the choroidals (see Fig. 4). The patient was cautiously placed on systemic Prednisone with Maalox and although the choroidal masses subsided, they did not completely disappear. The retina was



LOW LEVEL CHOROIDAL DETACHMENT
LARGE CHOROIDAL DETACHMENT
XII
XI
I
Attached Retina over choroidal detachment
O.D.
ORA SERRATA DISPLACED
Retinal TEAR
?
CHOROIDAL DETACHM.
RETINAL DETACH
IX
IV
Fixed RETINAL FOLDS
BULLOUS RETINAL DETACHMENT
VII
VI
V
Keith M. Zinn M.D.

FIG. 2. Fundus drawing illustrating a patient with a retinal detachment and multiple "choroidal detachments" or masses.

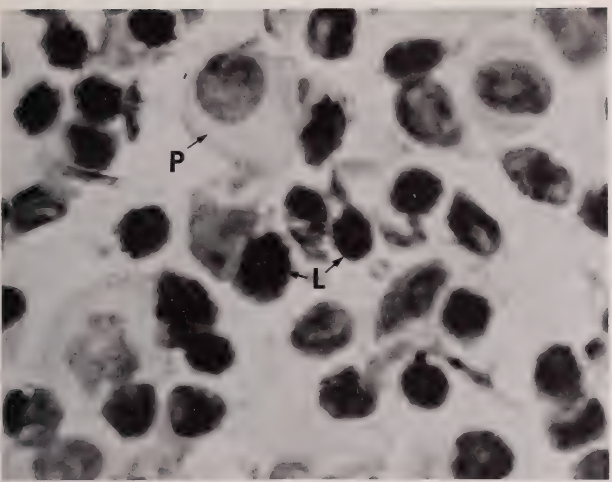


FIG. 3. Light micrograph of material obtained from one of the choroidal masses (suprachoroidal space) depicted in Fig. 2. Note the numerous lymphocytes (L) and plasma cells (P) Giemsa stain (×650).

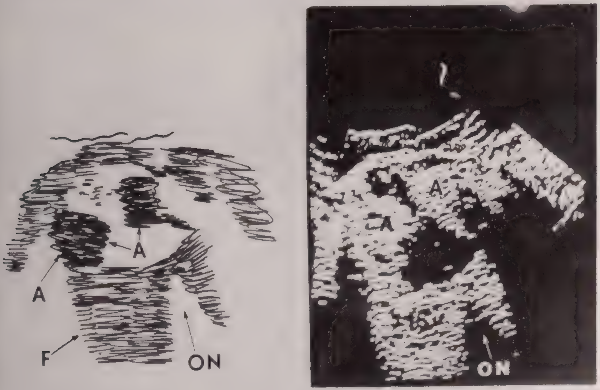


FIG. 4. B-scan ultrasonograph of the globe (horizontal section) in the same patient with choroidal masses (A) postop. retinal detachment surgery. The masses containing lymphocytes and plasma cells are solid on A and B scan ultrasonography. The retrobulbar fat patterns (F) and optic nerve (ON) shadow are acoustically within normal limits.

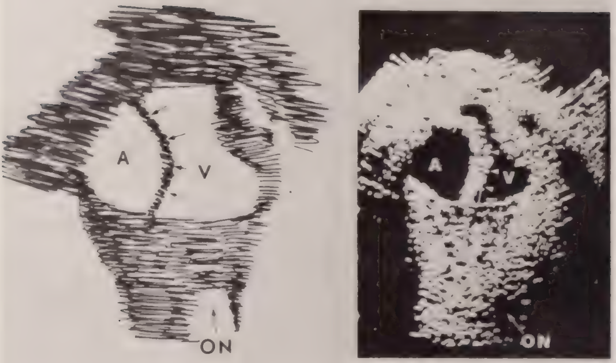


FIG 5. B-scan ultrasonograph of a globe (horizontal section) with a serous choroidal detachment (A) with convex walls (arrows) projecting into the vitreous cavity (V). Optic nerve (ON) shadow was acoustically normal.

reattached with scleral buckling surgery, but the steroids were essential to the reduction of the choroidal masses.

Discussion

The preoperative management of patients with choroidal and retinal detachments should begin with a careful examination of the retinal and choroidal tissues using indirect ophthalmoscopy with careful scleral depression and slit lamp biomicroscopy looking for retinal breaks, shifting subretinal fluid as well as cells in the vitreous cavity. Transillumination of the choroidal masses should be performed if possible. A Seidel Test for occult wound leaks in patients with a previous history of cataract and/or glaucoma filtering surgery should also be done. A and B scan ultrasonography should be performed to delineate the solid or fluid nature of the choroidal masses. This test can differentiate a serous (Fig. 5) versus hemorrhagic choroidal detachment. Ultrasonography can also detect localized tumors (Fig. 6) as well as ring melanomas.

If A and B scan ultrasonography reveals a serous choroidal detachment, then a trial of systemic steroids may be helpful preoperatively in reducing the choroidal detachments. Otherwise, drainage of the choroidal fluid (suprachoroidal space) may be necessary before proceeding with scleral buckling surgery. If the drainage is considerable, then it may be necessary to reconstitute the volume of the vitreous with injectable saline, via the pars plana, before proceeding with the repair of the retinal detachment. The major reason for

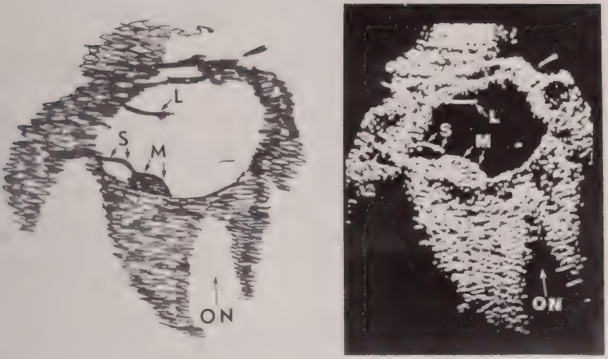


FIG. 6. B-scan ultrasonograph of a globe (horizontal section) with a choroidal melanoma (M) and a serous retinal detachment (S). The retrobulbar fat pattern outlines an acoustically normal optic nerve shadow (ON). The posterior lens capsule (L) is also outlined.

trying to reduce the choroidal fluid is to allow cryopexy and/or diathermy applications to get through to the inner choroid-retinal pigment epithelial layers so that a firm adhesion of the neurosensory retina to the retinal pigment epithelium (RPE) can develop post-repair of the retinal detachment and thereby, in effect, seal the retinal breaks.

If the preoperative ultrasound pattern indicates that the choroidals are solid, then the possibility of a melanoma must be ruled out and a P^{32} rest may be required along with a complete metastatic work-up, i.e., long bone survey, liver scan, 24 hour urine for melanin, etc. There are numerous other conditions that can give serous or solid choroidal detachments. For a complete discussion the reader is referred to the suggested bibliography.

In the case presented, a "normal" looking series of choroidal detachments was, in fact, a series of choroidal masses containing lymphocytes and plasma cells representing a rare condition termed reactive lymphoid hyperplasia of the uveal tract.

Preoperative A and B scan ultrasonography would have established the solid nature of the choroidals and perhaps a trial of systemic steroids might have reduced these choroidals making retinal detachment surgery easier to perform.

In summary, preoperative management of patients with simultaneous choroidal and retinal detachments (rhegmatogenous and nonrhegmatogenous) should include A and B scan ultrasonography to determine the nature of the choroidal detachments allowing for the proper approach toward reducing the choroidals so that successful reattachment of the retina can take place.

Suggested Reading

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Pediatric Notes

AARON R. RAUSEN, M.D., EDITOR

Psychological Maladjustment in a Child with Premature Pubarche

Submitted by
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ABSTRACT

Precocious pubarche in a young girl coupled with an adverse psychosocial environment led to aberrant behavior which responded dramatically to therapeutic intervention. This case emphasizes the vulnerability of a child with a constitutional variation and the importance of preventative referral for such children.

It is generally accepted that children with precocious sexual development may have psychological maladjustment minimized if properly managed (1, 2, 3, 4). However, as Thomas et al. point out, the extent to which precocious puberty may present a major problem may not yet be fully appreciated (5). The following is a case report of a child with premature pubarche, a condition far milder than precocious puberty, and the subsequent emotional difficulties she encountered. To our knowledge, this is the first report in the literature of the psychological and behavioral aspects of precocious pubarche. Precocious pubarche is not an uncommon condition, and although the exact incidence is unknown, there is a predilection for girls (6, 7). Similar principles of management may be of use in cases of organic anal, genital and rectal disorders.

Case Report

Medical

This female was first noted by her father to have pubic and axillary hair at 12 months of age, and by the child's pediatrician when she was 22 months of age. The amount had been slowly increasing. Family history was negative.

On physical examination, the blood pressure was 110/55, weight was 10.9 Kg. (25 percentile) and the height was 82.5 cm. (25 percentile). Many short straight black hairs were present over the labia majora and mons pubis with a moderate amount of black, downy fuzz over her upper lip. There was no clitoral hypertrophy. The labia minora were thin and undeveloped. The nipples were infantile. No mammary tissue was palpable. The remainder of the physical examination was normal. Examination of the patient's genitalia was repeated at three and then six monthly intervals with pediatric house staff present for teaching demonstrations.

Skull x-rays, wrist bone age, urinary 17-ketosteroids and 17-hydroxycorticosteroids were within normal limits.

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Psychological

The patient was referred for psychological management at 4½ years of age. Symptoms included exhibiting herself in nursery school, attempting to "show everyone her vagina" and self-directed aggression involving hitting and scratching herself until she bled. At the time of referral, the patient had just come to live with the father because her mother wanted to devote herself full-time to a writing and acting career. The child's symptoms were longstanding, but had intensified with this recent change. The parents had separated when the patient was 2 years old. During prior periods with her father, she frequently witnessed his nudity. He also dressed and bathed her, including washing her genitals. Various girl friends of the father lived at the apartment and, on occasion, the child expressed jealousy about them.

The child entered weekly psychotherapy and the father weekly counseling sessions. Both were seen by the same therapist (L.D.). As therapy progressed, it became apparent that the child's preoccupation with sexual matters was for the most part due to sexual overstimulation by her father. To a lesser extent, medical focusing on her genital area may have caused additional stress. This was evidenced by play therapy sessions in which she reenacted genital examinations in a manner that indicated they were frightening to her.

Psychological testing after three months of therapy revealed an I.Q. of 124 on the Stanford-Binet test. Test results did not suggest organicity, thought disorder or breaks in reality testing. The diagnosis was Adjustment Reaction of Childhood.

Intensive therapeutic sessions with the father and child resulted in dramatic symptomatic improvement. Self-directed aggression and exhibitionism ceased. The patient became appropriately modest for her age. The mother refused to participate in counseling sessions.

Comment

Her premature pubarche aside, this child probably would have had emotional problems due to the disturbed family situation. However, the physical abnormality intensified and complicated her other problems.

First, from a developmental point of view, the age at which this was brought to medical attention is important. At 22 months, the child is normally becoming more aware of her own genitals and the difference between girls and boys (8). In this case, a great deal of attention was given to the early development of pubic hair. Numerous examinations were done with pediatric house officers. This patient's symptom of showing her vagina may have been in part an attempt to master anxieties associated with repeated medical examinations and to gain reassurance about her physical condition. Physicians should exercise caution about demonstrations of this sort. In this patient's case the examinations and demonstrations, although of course not the major cause of her problem, probably intensified the difficulty.

Also, at about this age, the young child is establishing her gender identity. In the sexually precocious girl, this involves not only the adjustment to think of herself as a girl or boy, but as a girl or woman. The development of pubic hair may have confused this patient and inappropriately reinforced her identification with her mother and then later, her desire to compete for the attentions of her father.

Regarding family pathology, her condition also appears to have dovetailed with the pathology of her father. The father, a disturbed man with schizoid adjustment, had unconscious needs to view his daughter as a marriage partner. These needs were intensified by his daughter's pubic hair.

We have limited our discussion to the possible psychological effects of precocious pubarche and how this condition interwove with the patient's other problems. Concerning medical management, we suggest limiting patient demonstrations. This could be accomplished by use of a photograph for future teaching. Further examinations (as by a consultant) should be complete and not focus on the anal-genital area alone.

Conclusion

A case of a 2 year old girl with premature pubarche and associated emotional difficulties is presented. Despite this child's many problems, she responded very well to intervention in a relatively brief period.

Anatomical or constitutional problems of the anal-genital area in children may be sensitizers to latent psychopathology in the family. We recommend preventive referral for evaluation of all such children and their parents. Reassessment at periodic intervals is vital to detect current emotional problems. In addition, physicians should limit teaching demonstrations and examinations of children with anal-genital disorders so as to minimize reinforcement of anxieties.

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Student Section

Hepatoma with the Complication of Spontaneous Rupture and Hemoperitoneum: Case Report and Discussion

CHARLES CAMISA, M.D.

In the United States and Europe, primary carcinoma of the liver is a relatively rare disease occurring in 0.2 to 0.7% of all autopsies (1) and accounting for 0.75% of all cancer deaths (2). About 90% of these tumors are hepatocellular carcinomas (hereafter called hepatomas); the remainder are cholangiocarcinomas, mixed hepatocholangiocarcinomas, and the rare sarcomas (3). It affects men more frequently than women, with ratios varying from 2.5 to 5:1, and the ages of peak incidence are the sixth and seventh decades (1, 3, 7).

There is a significant association between all varieties of cirrhosis and hepatoma. Approximately 60% (55 to 69%) of all hepatomas are associated with cirrhosis (1, 3, 5, 7). This figure may reach 90% in hospitals with high alcoholism admission rates (2) since 4% of cirrhotics develop hepatoma (1). Autopsies usually disclose extensive extrahepatic metastatic disease, most commonly to lungs, intraabdominal lymph nodes, adrenal glands, great veins adjacent to liver, and skeleton (1, 2, 4, 5). Life expectancy averages roughly six months to one year from onset of symptoms and 3–6 months from diagnosis (2).

Microscopically, the most useful feature in establishing the diagnosis of hepatoma is the similarity of tumor to normal liver cells and their trabecular structure. The tumor cells, however, are larger than normal with abundant dense eosinophilic cytoplasm, large ovoid or irregular nuclei and large eosinophilic central or eccentric nucleoli. Mitotic figures are common in some fields, and multinucleated tumor giant cells containing typical or bizarre irregular and dense nuclei may be seen (4). Although histology varies from remarkable resemblance to normal liver to totally anaplastic, it is not now possible to differentiate these tumors according to prognosis since the range of patient survival is so limited (11).

Roentgenologically, chest x-ray may reveal evidence of osseous, pulmonary or pleural metastatic disease (8). The right hemidiaphragm may be elevated (2). Upper gastrointestinal and barium enema studies are intrinsically normal but may show evidence of extrinsic compression from tumor masses. Gastric displacement is noted more often anteriorly than inferiolaterally when present.

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In general, all celiac arteriograms are interpreted as showing evidence of tumor in the liver (2, 6). The occurrence of a vascular mass with tumor vessels, a prolonged vascular blush, stretching and displacement of hepatic vessels, and arteriovenous shunt formation (early draining veins) strongly suggests the diagnosis of hepatoma (2). If the patient has widespread liver metastases with marked vascular proliferation, differentiation becomes difficult if not impossible (12).

The most frequent clinical presentation of hepatoma consists of right upper quadrant or epigastric pain and palpable mass with anorexia and weight loss, and accumulation of ascites or jaundice. Liver function tests are abnormal in most patients (7) and elevated alkaline phosphatase may be the earliest indicator (5). Notwithstanding, the diagnosis of hepatoma is infrequently made clinically. In one series (1) only 7/60 were diagnosed clinically, and hepatoma was included in the differential in 30% of 164 histologically diagnosed cases in another (4). Certainly the diagnosis must be considered in the setting of clinical deterioration of a known cirrhotic. In fact, any liver mass should be considered hepatoma in this setting until proven otherwise because of the striking association between hepatoma and cirrhosis alluded to previously and because metastatic disease to cirrhotic liver is uncommon. Many atypical presentations of hepatoma have been reported: hematobilia, acute cholecystitis, fever with necrotic tumor abscess, acute hepatic and renal failure, Budd-Chiari syndrome, malignant plural effusion, pathologic fracture of metastatic bone lesion, obstructive jaundice, recurrent hepatitis, the various paraneoplastic syndromes (not unique to hepatoma), and massive intraperitoneal hemorrhage from spontaneous rupture of hepatoma. The following is a case report of a hepatoma presenting in this last mode in an elderly man.

Case Report

M. M., a 76-year-old black man was admitted to the medical service at City Hospital Center at Elmhurst on 7/26/76 with abdominal cramps, nausea and vomiting, and generalized weakness for one day. Fourteen months prior to this admission he underwent perineal prostatectomy and orchiectomy for adenocarcinoma of the prostate. He had been taking 1 mg. of stilbestrol daily since the operation. He was apparently well until the day of admission. He denied weight loss, hematemesis, blood per rectum, melena, and history of trauma. He gave a history consistent with excessive alcohol intake many years ago.

On admission physical exam revealed an alert chronically ill elderly man in moderate distress. T97.6, P92 R20 BP90/50. There was no scleral icterus, the conjunctivae were pale, tongue dry, significant gynecomastia, lungs clear, a 2/6 SEM heard at left sternal border, tenderness of the right flank and scapular area, a palpable liver edge, tenderness in the right upper quadrant with voluntary guarding and decreased bowel sounds. Spider angiomata, palmar erythema, and asterixis were not present.

His CBC revealed a hematocrit of 26%, hemoglobin of 6.8gm.%, white count of 11,900/cmm. with 83 segs, 5 bands, and 12 lymphs. The red blood cells were hypochromic and microcytic. SMA 18: Na 140, K 5.1, Cl 105, CO_2 26, BUN 23, glucose 150, cholesterol 207, uric acid 10, creatinine 2.1, total bilirubin 0.5, alkaline phosphatase 157 IU, LDH 985 IU, SGOT 410 IU, and amylase 115 Dye U. The prothrombin time was 12.6 seconds with a control of 11.4 seconds. A chest X-ray was normal. A plain film of the abdomen revealed calcifications at T12 in the area of the gall bladder and questionable lytic lesion of L5 (Fig. 1).

His hospital course was marked by changing abdominal physical signs and symptoms. He was given 3 units of packed red blood cells. On the third hospital day, he was transferred to the surgical service when his abdomen became moderately distended and silent with generalized guarding and rebound. A perforated viscus was suspected, but emergency gastrograffin meal and enema were read as normal. (In retrospect, there was inferolateral displacement of the stomach. Fig. 2) A diagnostic paracentesis revealed gross blood in the peritoneal cavity.

An aortogram and celiac arteriography were performed to help localize the bleeding site prior to surgical intervention. In the liver it showed neovascularity, tortuous vessels, miliary blush of entire right lobe, multiple AV fistulae, and a cystic vascularized mass in lower pole of right lobe (Fig. 3).

At laparotomy blood was aspirated from the peritoneal cavity. The liver appeared cirrhotic and

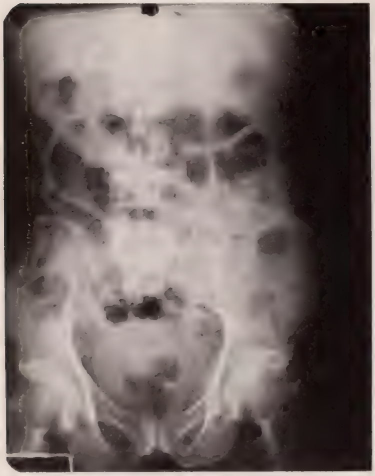

FIG. 1. Plain film of abdomen on admission shows normal gas pattern, distended bladder, and calcifications in the right upper quadrant which were actually in the cystic necrotic tumor mass.

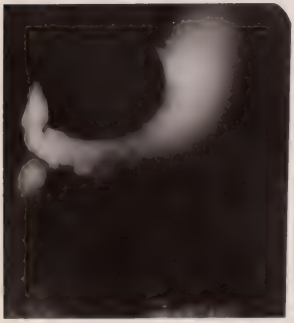

FIG. 2. Film from gastrograffin meal shows extrinsic compression of the lesser curvature of the stomach.

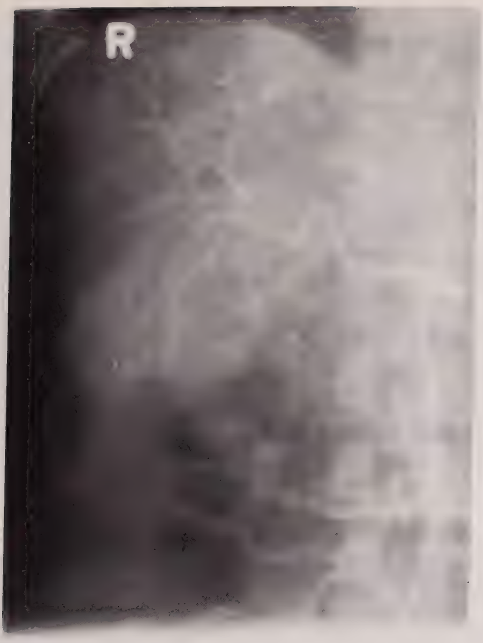

FIG. 3. Selective right hepatic arteriogram shows tortuous vessels, miliary blush of entire right lobe, and relatively lucent cystic mass in lower pole.

filled with yellow white firm nodules. There was a cystic necrotic mass (in lower pole of right lobe) with dilated veins on its surface which were oozing, the obvious source of hemorrhage. Biopsy of this area and another were obtained and hemostasis was secured with gelfoam. Histologic examination revealed that the liver parenchyma was replaced by nodules composed of irregularly placed cells with large pleomorphic hyperchromatic nuclei, prominent nucleoli, some forming multinucleated giant cells with abundant eosinophilic cytoplasm, many containing Mallory (alcoholic hyalin) bodies, consistent with hepatocellular carcinoma Figs. 4 & 5).

The patient became progressively anorexic, jaundiced, and distended with ascites. He died 45 days after surgery.

Discussion

Papers on spontaneous rupture of hepatoma in occidental literature are mainly limited to case reports (8–10). But this presentation is fairly common in African sub-Saharan countries and among the Chinese in South China and Hong Kong where the incidence of hepatoma exceeds that in the U.S. and

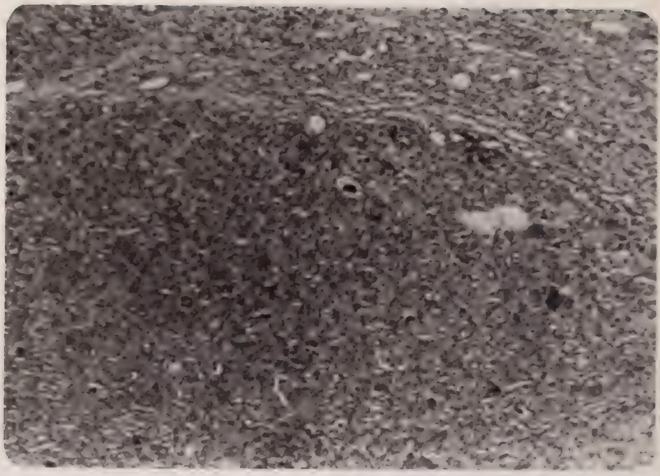

FIG. 4. Low power view of histologic section of a nodule of hepatocellular carcinoma shows superficial resemblance to liver with loss of normal trabecular architecture.

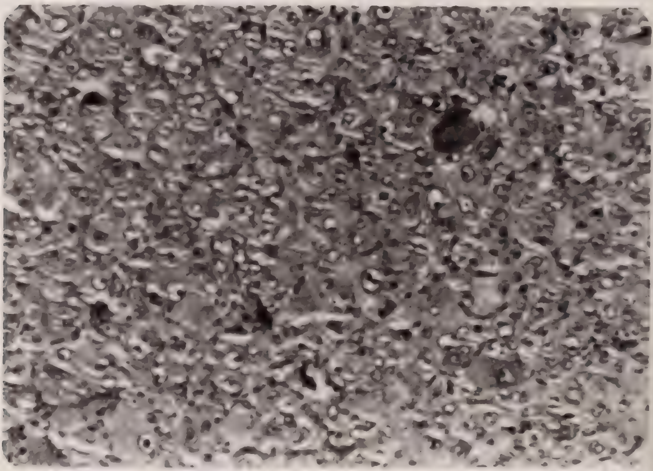

FIG. 5. High power view of section of hepatocellular carcinoma shows loss of polarity of tumor cells with large pleomorphic hyperchromatic nuclei and prominent nucleoli. Multinucleated tumor giant cells with abundant eosinophilic cytoplasm and Mallory bodies are also present.

Europe by 5–25 fold, the age peak is two decades younger, and the clinical diagnostic accuracy is high (86.5%). In Uganda, Alpert et. al. (5) report 46 cases of hepatoma in 9 months, 5 of which (11%) presented as acute hemoperitoneum. In the series of Ong et. al. (6) in Hong Kong, 15/117 or 13% had intraperitoneal hemorrhage secondary to rupture of hepatoma.

It is most difficult to make the diagnosis when the patient was apparently healthy prior to onset of pain. The most frequent error made is the diagnosis of perforated gastric or duodenal ulcer (6) as was done in the case under discussion. The clinical features of spontaneous rupture of hepatoma are 1) sudden onset of severe pain in the right upper quadrant which becomes generalized, 2) shock, 3) signs of peritoneal irritation and 4) blood in the peritoneal cavity.

Several hypotheses of pathogenesis of rupture of hepatoma exist: 1) The tumor infiltrates and gradually obstructs its venous drainage system (portal). If this happens before collateral subcapsular branches of the hepatic vein open up, a tamponade effect is produced followed by rupture and bleeding. 2) Minimal trauma may rupture a surface tumor. 3) Rupture may occur from the center of a necrotic tumor by erosion of blood vessels. 4) Cystic lesions (as in this case and 2 previously reported (8)) may rupture from increased intrahepatic vascular tension.

In management of acute hemoperitoneum secondary to rupture of hematoma, it is necessary to prepare the patient for exploratory laparotomy with intravenous fluid and blood replacement therapy to raise blood pressure. At operation, depending on extent of tumor and condition of patient, some attempt should be made to enucleate the tumor, evacuate necrotic tumor, or resect the involved lobe (where advanced cirrhosis is a contraindication) and establish hemostasis with suture or packing. With any treatment the prognosis remains bleak: 18/20 patients in Ong et. al.'s (6) series were dead within 6 months.

Two miscellaneous points deserve mention in this discussion. When the unsuspected hepatic tumor was noted during celiac arteriography without a bleeding site, the catheter was placed in the right hepatic artery, again to no avail. The tumor, due to its vascularity, was assumed to be the site of hemorrhage. The diagnostic difficulty for the radiologist was in deciding whether the neoplasm was a primary or secondary hepatic process since the patient had a known prostatic carcinoma. In the Memorial Hospital series, 9/67 (13.4%) patients with hepatoma had a pathologically proved second malignant tumor, none of which was prostate; 6/60 (10%) had a second malignancy in the Detroit series (1), and three were of prostate.

Finally, although hepatoma is known to be associated with long-term administration of androgenic-anabolic steroids (16), recent concern has been directed toward the association of synthetic estrogens with an increased incidence of benign hepatic neoplasms, often with spontaneous rupture and hemorrhage (13–15). One case of hepatoma in a young woman on the birth control pill has been reported (14). Perhaps it is relevant that the male patient in the case under discussion was taking 1 mg. stilbestrol for over one year.

Summary

The incidence, pathology, roentgenology, and clinical presentation of hepatocellular carcinoma are reviewed. A case of hemoperitoneum secondary to spontaneous rupture of hepatoma is presented with a discussion of the incidence, diagnosis, pathogenesis, and management of this complication.

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550 Cases of Prenatal Cytogenetic Diagnosis: Experience and Prospects*

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Introduction

Since 1966, the technique of culturing amniotic fluid cells has been developed and improved (1,2,3). The cultivated amniotic fluid cells have been used for both cytogenetic and biochemical studies (4,5,6). Various genetically determined disorders can now be prenatally diagnosed; hence, birth of such affected children can be prevented. However, the greatest demand has always been for prenatal cytogenetic diagnosis. This paper will report the results of our first 568 cytogenetic cases collected in six years experience in prenatal diagnosis, 550 of which resulted in successful diagnosis.

Materials and Methods

From 1969 to the end of 1974, we have studied 584 diagnostic amniotic fluids. Of these, 536 (91.5%) were primarily for cytogenetic diagnosis. Cytogenetic studies were also carried out in 16 cases in which amniocentesis was performed primarily for prenatal biochemical diagnosis and 16 cases where prenatal detection of neural tube defects was the prime concern. Cytogenetic studies were done in a total of 568 cases. Transabdominal amniocenteses were done between 14 and 20 weeks of gestation with the majority between 16 and 17 weeks. Ultrasonic localization of the placenta was used prior to amniocentesis in 70% of the cases. The volume of amniotic fluid ranged from 8 ml to 35 ml with the majority between 20 and 30 ml. The amniotic fluid cells were cultivated according to the method reported from this laboratory (3).

Routinely, a total of 20 good metaphases of the cultured amniotic fluid fibroblast cells from at least two tissue culture flasks was examined and three conventional karyotypes were made for each case. Quinacrine fluorescence staining (Q-banding) (7, 8) and/or trypsin Giemsa banding (G-banding) (8, 9) was carried out in cases where further identification of numerical or structural aberration as well as confirmation of normal variants was indicated. Since 1971, either Q or G-banding was employed in all cases where one of the parents

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was a translocation carrier and all cases with a history of fetal wastage, stillbirth(s) or child(ren) with multiple anomalies. In order to diagnose mosaicism, multiple tissue culture flasks were used for harvest. If one tissue culture flask showed a numerical or a structural aberration, more cells (up to a total of 40–50 cells) of this flask were examined to assess the frequency of this abnormality. If the same abnormality was detected more than one time from one flask, harvests from different tissue culture flasks were carried out. Diagnosis of mosaicism was made only when each different flask showed cells with the same abnormality. In cases with normal chromosome variants, we have also studied the chromosomes of both parents with the banding techniques for further confirmation of the origin of the normal variant.

The indications for prenatal diagnosis of the 550 successful cases are listed in Table I. 305 were for advanced maternal age. Of these, 169 were in women 40 years and over at estimated expected date of confinement, and 107 were between 37 and 39 years. 29 were 35 or 36 years. 127 cases had a previous child with Down's syndrome. Seven were for detection of a translocation because one parent was a translocation carrier. Twenty had a previous child with multiple congenital anomalies. Eight had a previous child with trisomy 18 or 13. Four pregnancies were monitored because of paternal trisomy mosaicism and a previous child with such trisomy. Other miscellaneous reasons for cytogenetic diagnosis included drug users (LSD and methotrexate), parental exposure to X-irradiation, family history of Down's syndrome and parental anxiety. Eleven had previous sons with an X-linked recessive disorder and requested prenatal sex determination. For this group, karyotype analysis of the cultured amniotic fluid fibroblasts was employed in ten of the eleven cases, since we found that determination of X-chromatin and Y fluorescent bodies in the uncultured amniotic fluid cells is not accurate (10).

Results

Chromosome analysis was successful in 550 cases including 518 cases done for prenatal cytogenetic diagnosis and 32 cases studied for other purposes (16 for biochemical studies and 16 for prenatal detection of neural tube defects). For completeness, we have included 325 successful cases previously reported from our laboratory (6, 10). Four per cent (i.e., 22 cases) of the successful cases required a repeat amniocentesis because the first culture was not successful. There were 18 unsuccessful cases where a repeat amniocentesis was refused. Thus the overall failure rate of the first culture was 7.5%. Of these 18 unsuccessful cases, 11 gave birth to normal live infants, one (age 41) had a child with Down's syndrome, two were carrying fetuses which were apparently dead before amniocentesis, one was aborted later as a macerated fetus, one was born prematurely but without congenital abnormality, and two were lost to follow up.

No differences have been observed in terms of growth rate between those amniocenteses monitored by ultrasonic localization of the placenta and those not so monitored. However, there was a difference in the frequency of bloody taps in the two groups. Without sonogram bloody taps were observed in 19.5%

TABLE I

Successful Cytogenetic Studies in 550 Amniocentesis

Indication	No.		Result: Normal		Trisomy	Mosaicism	Other
Advanced maternal age	305		292		11*	2*	
40 yrs. & over		169		162	7*(4–47, +21; 2–47, +18; 1–XXY)	0	
37–39 yrs.		107		102	4*(2–47, +21; 1–47, +18; 1–48, XYY,+21)	1*(XO/XX)	
35–36 yrs.		29		28	0	1*(XO/XY)	
Previous child with Down's syndrome	127		125		1*	1*	
<35 yrs.		98		98	0	0	
35–36 yrs.		7		7	0	0	
37–39 yrs.		10		10	0	0	
40 yrs. & over		12		10	1*(47, +21)	1*(46/47, +20)	
Previous child with multiple anomalies	20		20		0	0	
Translocation carrier	7		6		0	0	1 (45, −14, +t (21q14q) balanced carrier
Centric fusion		3		2	0	0	
Reciprocal		4		4	0	0	
Previous child with trisomy 18 or 13	8		8		0	0	
Paternal trisomy mosaicism	4		4		0	0	
46/47, +21		3		3	0	0	
46/47, +18		1		1	0	0	
Others	36		35		0	0	1 (46, 13p−)
Biochemical studies	16		16		0	0	
Neural tube defect	16		16		0	0	
X-linked disorders	11		3 (46,XX)		0	0	8 (46, XY; 7*)
Total	550		525		12*	3*	10 (7 cases*)

* Therapeutic abortion

(35/178 taps) whereas with sonogram, bloody taps were seen in only 8.4% (33/392 taps).

Of the 550 successful cases, 22 mothers (marked with an asterisk in Table I) elected to have a therapeutic abortion, 15 on the basis of prenatal cytogenetic diagnosis and 7 on the basis of prenatal diagnosis of a male fetus at risk for an X-linked recessive disorder. The results of the prenatal cytogenetic findings are shown in Table I. By combining the patients where the indication was advanced maternal age (305 cases) and those 35 years and over studied because of a previous child with Down's syndrome (29 cases), a total of 334 mothers of 35 years and over had successful prenatal cytogenetic diagnoses in which 12 trisomies were found. In 181 cases of 40 years and over including 12 cases with previous Down's syndrome, 8 cases of trisomy (including 5 cases of trisomy 21, 2 cases of trisomy 18 and 1 case of 47,XXY) were diagnosed. Of the 5 cases of trisomy 21, one mother had a previous child with Down's syndrome. In 117 cases where maternal age was 37 to 39 years (including 10 with previous Down's syndrome), 4 cases of trisomy (including 2 cases of trisomy 21, 1 case of trisomy 18 and 1 case of double trisomy, XYY and 21) were detected. In 36 cases of maternal age 35 and 36 years including 7 cases with previous Down's, no case of trisomy was detected. The case of double trisomy 48,XYY,+21 in the advanced maternal age group was diagnosed from a 38 year old mother. The double trisomy was identified by both quinacrine fluorescent and trypsin Giemsa banding techniques. Hypertonic saline abortion was performed in the 20th week of pregnancy. The abortus was a male fetus weighing 225 gms and measuring 16 cm in crown-rump length and showed many features of trisomy 21. A detailed description of this case is reported (11).

In the group of advanced maternal age from 35 to 39 years, there were 2 cases of 45,X mosaicism, i.e., one of 45,X/46,XY and one of 45,X/46,XX. The diagnosis of mosaicism of 45,X/46,XY was made from two amniotic fluid cultures, since only 45,X cells were recovered from the first culture, although from three separate tissue culture flasks, and only 46,XY were found from the second culture. The abortus was a phenotypic male with no gross abnormality. A detailed description of this case was reported by Kardon et al. in 1972 (12). The diagnosis of 45,X/46,XX mosaicism in the second case was made by finding the same type of mosaicism in multiple tissue culture flasks of the amniotic fluid cell culture (Table II). The 45,X cell line was identified by trypsin G-banding. The mother was 38 years of age. The mosaicism was found again in seven tissue culture flasks of the amniotic fluid obtained immediately before the saline abortion at 21 weeks of gestation (Table II). The abortus was a phenotypic female fetus, measuring 29 cm in length and weighing 430 gm. There was no gross abnormality phenotypically or internally. The fetal tissue failed to grow in tissue culture because of severe maceration due to hypertonic saline abortion.

In 127 pregnancies with a history of a previous child with Down's syndrome, one recurrence of trisomy 21 was found in a 40 year old mother. This represents a recurrence risk of 0.78%. In this group, there was also a prenatal cytogenetic diagnosis of 46,XX/47,XX,+20 in a mother of 41 years of age. The trisomic

TABLE II

Results of Culture of Amniotic Fluid Cells in case of 45,X/46,XX Mosaicism

	Tissue Culture Flask No.		No. of Cells with 45,X (%)		No. of Cells with 46,XX (%)		Total No. of cells examined
First amniotic fluid cell culture at 16th week of pregnancy	A	1st harvest	19	(90.5%)	2	(9.5%)	21
		2nd harvest	12	(70.6%)	5	(29.4%)	17
	B		5	(14.3%)	30	(85.7%)	35
	C		2	(4.0%)	48	(96%)	50
		TOTAL	38	(30.9%)	85	(69.1%)	123
Second amniotic fluid cell culture (before hypertonic saline instillation)	E		1	(5%)	19	(95%)	20
	F		9	(45%)	11	(55%)	20
	G		2	(10%)	18	(90%)	20
	H		2	(9.5%)	19	(90.5%)	21
	I		3	(15%)	17	(85%)	20
	J		13	(65%)	7	(35%)	20
	K		2	(10%)	18	(90%)	20
		TOTAL	32	(22.7%)	109	(77.3%)	141

TABLE III

Results of Culture of Amniotic Fluid Cells in case of 47,XX,+20/46,XX Mosaicism

	Tissue Culture Flask No.	Chromosome Constitution				
		47,XX,+20	(%)	46,XX	(%)	Total
First amniotic fluid cell culture at 16 weeks of pregnancy	A	2	(4%)	48	(90%)	50
	B	4	(20%)	16	(80%)	20
	Total	6	(85%)	64	(91.5%)	70
Second amniotic fluid cell culture at 20 weeks of pregnancy (before hypertonic saline instillation)	C	0		26	(100%)	26
	D	0		100	(100%)	100
	E	0		9	(100%)	9
	Total	0		135	(100%)	135

cells were recovered from two separate tissue culture flasks (Table III). The extra chromosome in the cells with 47 chromosomes was identified to be a No. 20 by Q- and G-banding from both tissue culture flasks (Fig. 1). A therapeutic abortion with hypertonic saline was carried out at 20 weeks of pregnancy. The abortus was a female fetus, measuring 27 cm in length and weighing 370 gms with no gross anomalies. From the amniotic fluid obtained before the saline abortion, a total of 35 cells was examined from 3 different tissue culture flasks and no cells with 47,XX,+20 were recovered. The fetal tissue failed to grow in tissue culture due to severe maceration.

All twelve trisomic abortuses had typical pathologic features for such trisomy. The details of one case of trisomy 21 from a mother with a previous child with Down's syndrome, one case of 47,XXY, and one case of trisomy 18 in the maternal age group of 40 years and older were reported previously (10, 13). Further cytogenetic confirmation from the cultured fetal tissues was possible in one trisomy 18 and one trisomy 21 case after hysterotomy abortion. All other abortions were performed with hypertonic saline instillation which resulted in macerated fetuses and provided no viable fetal tissue for culture.

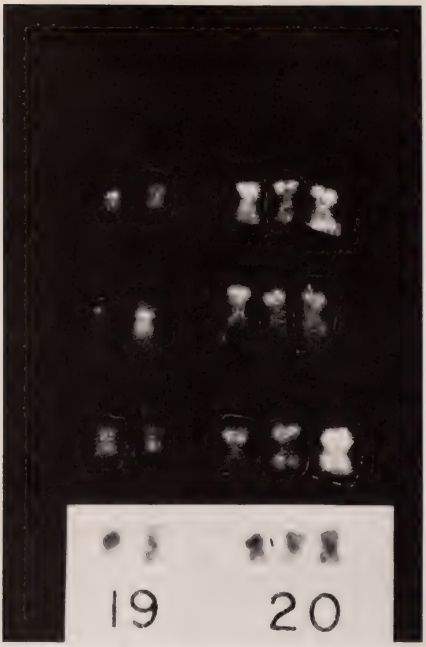

FIG. 1. Case of 46,XX/47,XX,+20 mosaicism. Quinacrine banding patterns (upper 3 rows) and Giemsa banding patterns (bottom row) of four partial karyotypes of chromosomes No. 19 and 20, showing trisomy 20.

We were able to do dermatoglyphic analysis in the two cases of hysterotomy abortions and one other trisomy 21. Both fetuses with trisomy 21 showed typical dermatoglyphic patterns for Down's syndrome; the case of trisomy 18 showed 3 arches, 6 ulnar loops and one radial loop on the finger tips and distally located axial triradii bilaterally.

No recurrence was found in the 8 mothers with a history of a previous child with trisomy 18 or 13. In the group where one of the parents was a translocation carrier, only one, a case of balanced centric fusion type of translocation, was found in the fetal cells. Since balanced centric fusion type of translocation is associated with normal phenotype, the parents decided to continue the pregnancy, which resulted in a clinically normal female infant. In the 4 cases of paternal mosaicism, no recurrence was found. In the group done for other reasons, one fetus was found to have a short arm deletion of a No. 13 chromosome. A similar structural abnormality was also detected in the phe-

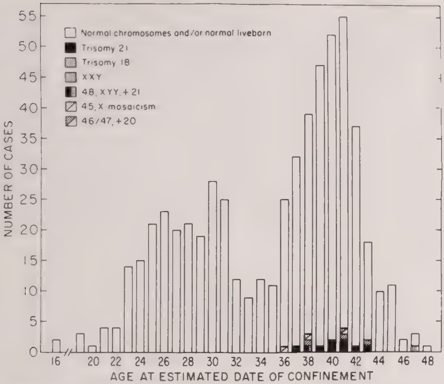

FIG. 2. Age distribution of cases monitored by amniocentesis, indicating those cases with chromosomal aberrations.

TABLE IV

Known Trisomies in Pregnancies Monitored with Amniocentesis, Classified by Maternal age

Maternal age	Nos. of pregnancies monitored with amniocentesis	(Cases with successful cytogenetic studies)	Trisomy all types (%)		Trisomy 21 (%)	
40 years & over	189	(181)	9	(4.76%)	6	(3.17%)**
37–39 years	118	(117)	4	(3.38%)	3	(2.59%)***
35–36 years	36	(36)	0		0	
<35 years	232	(216)	0		0	
TOTAL	575*	(550)	13		9	

* This total includes all cytogenetic and non-cytogenetic cases with known maternal age and known outcome of the pregnancy; 9 other cases of unclear maternal age or unknown outcome of the pregnancy were not included in this table.

** One mother had a previous child with trisomy 21, and one case was diagnosed at birth since the prenatal cytogenetic diagnosis from the amniotic fluid cell culture was not successful and the mother refused to have a second tap.

*** These three cases of trisomy 21 include one case with double trisomy, 48,XYY,+21.

notypically normal mother and several other maternal relatives. This baby was born with clinical Noonan's syndrome.

In the group of X-linked disorders, 8 mothers were found to be carrying a 46,XY fetus. Seven requested therapeutic abortion because of the 50% risk of bearing another affected son. One XY fetus was at risk for being affected with X-linked Schilder's disease. Since the biochemical studies of the cultured amniotic fluid cells by Dr. Henry Nadler indicated the likely possibility of a normal fetus, the parents decided to continue this pregnancy. The Y chromosome of this case was a partially deleted Y(Yq-) with no fluorescent band, also found in the father. In fact, no fluorescent body, nor an X-chromatin body was detectable in the uncultured amniotic fluid cells. This emphasizes again that prenatal sex determination cannot rely on X-chromatin or Y fluorescent body determination in the uncultured amniotic fluid cells.

In the 550 cases of successful prenatal cytogenetic diagnosis, enlarged satellites of acrocentric chromosomes were observed in 20 cases (3.6%) with Ds+ in 10 cases and Gs+ in 10 cases. In 292 XY amniotic fluids, Yq+ was seen in 3 cases (1%), Yq− in 3 cases (1%) and inv Y(p+q−) in 1 case (0.34%). In 9 cases (1.6%), 2–5% of cells were found to have an extra chromosome detected in only one of several tissue culture flasks. In 4 cases (0.7%), a small proportion of cells from only one tissue culture flask was found to have a structural aberration. Chromosomal mosaicism was not considered in these 13 cases.

In our series, we have rarely found more than 20% tetraploid cells. However, we have found one case in which the second harvest showed 71% tetraploids. Since the case reported by Kohn and Robinson (15), where a therapeutic abortion was performed after the finding of 83% tetraploid cells and a chromosomally normal fetus was aborted, we have not been alarmed by this problem.

TABLE V

Outcome of 568 Cases Monitored by Prenatal Cytogenetic Diagnosis

Outcome	Cases with Successful Prenatal Cytogenetic Diagnosis	Cases with Unsuccessful Prenatal Cytogenetic Diagnosis	Total
Normal live infant, term pregnancy	469 (including 2 pairs of twins)	11	480
Normal live infant, premature birth	5	1	6
Premature birth and death due to prematurity	4	0	4
Therapeutic abortion	23	0	23
Induced abortion due to other reasons	6	0	6
Spontaneous second trimester abortion	8	0	8
Spontaneous abortion due to maternal diabetes	1	0	1
Fetal death in utero	5	1	6
Fetal death before amniocentesis	0	2	2
Stillbirth	5	0	5
Neonatal death	1	0	1
Child born with anomalies	6	1 (Down's syndrome)	7
Noonan's-1; Congenital heart disease-1; Unilateral renal agenesis-1; Microphallus & hypospadias-1; Funny looking kid-1; Club foot-1	(1 each)		
Lost to follow-up	19	2	21
TOTAL:	552 (including 2 pairs of twins)	18	570

In reviewing all our cases where a diagnostic amniocentesis was done, the 575 pregnancies with known maternal age were tabulated in terms of cytogenetic diagnosis and/or outcome of pregnancy (Figure 2). 189 were 40 years and over; nine cases of trisomy (4.76%) were found in this group including six cases (3.17%) of trisomy 21 (Table IV). In 118 mothers aged 37 through 39, four trisomies (3.38%) were found; these included three cases of trisomy 21 (2.59%) (Table IV). No trisomy was detected in mothers aged 36 and under.

The outcome of 550 pregnancies with successful prenatal cytogenetic diagnosis as well as 18 pregnancies with unsuccessful prenatal cytogenetic diagnosis due to no growth of the amniotic fluid cells is shown in Table V.

Discussion

We have presented the results of our first 550 successful cases of prenatal cytogenetic diagnosis. In a total of 584 pregnancies monitored for all purposes by mid-trimester transabdominal amniocentesis, we have observed no maternal morbidity or mortality. Out of 568 cases monitored for cytogenetic reasons, the outcome of the pregnancy was known in 547 cases (Table V). In this series of 547 cases, there were 9 spontaneous second trimester abortions (the maternal ages were 25, 31, 37, 38, 40, 41, 42, 43 and 43), 6 deaths *in utero* (maternal ages of 28, 28, 30, 37, 38, 40) and 5 stillbirths (maternal ages of 33, 38, 42, 42, 48).

In a report by Shapiro et al. (16), 13.37% of 9696 pregnancies of maternal age under 35 years resulted in fetal death; 6.66% of fetal loss was below 12 weeks gestation, 4.81% between 12 and 19 weeks, and 1.89% at 20 weeks or over. In the maternal age group of 35 years or over, however, 23% of 1923 pregnancies resulted in fetal deaths. Of these, 13.4% were below 12 weeks gestation, 6.8% were between 12 and 19 weeks, and 3.2% were 20 weeks or over. In a recent report by Cantu et al. (17), 2.2% of 184 pregnancies of women over 40 years of age ended in stillbirths. In our series ten of 14 cases including both second trimester spontaneous abortions and deaths in utero, were 37 years and over, as were the maternal ages in four out of five of the stillbirth group. Thus the percentage of fetal loss after mid pregnancy in our series of 304 mothers over 37 years (Figure 2), is 3.2% (10/304), and the frequency of stillbirth is 1.3% (4/304), similar to the incidence in the other studies without amniocentesis (16, 17). The results with amniocentesis apparently are not significantly different from what might be expected in this age group without amniocentesis, even including one 42 year old mother who aborted shortly after amniocentesis because of amnionitis resulting from repeated amniocentesis by an inexperienced obstetrician.

Two of the five fetal losses in the younger maternal age group (below 35 years of age) were due to obvious reasons. One 30 year old woman had a death in utero because of sudden onset of severe diabetes, and one abortus from a 31 year old mother showed a severe central nervous system defect. Thus, in our series, there were 3 fetal losses in pregnant women under 35 years of age; this represents a frequency of 1.3% (3 out of 232 mothers in this group) again not different from a group studied without amniocentesis (16).

In comparing the outcome of 101 pregnancies with amniocentesis and 104 control pregnancies without amniocentesis (Table VI), (6), there was only one spontaneous abortion which was clearly the result of multiple repeated amniocentesis by an inexperienced obstetrician. There was no increased frequency of premature birth or stillbirth in the pregnancies with amniocentesis. The infants of both groups have been reexamined at one year of age in order to determine whether any long range developmental problems are related to amniocentesis. Until now, no differences have been observed between the two groups of children.

Our studies showed an affected rate of 4.76% for all trisomies and 3.17% for trisomy 21 alone in the advanced maternal age group 40 years and over; 3.38% for all trisomies and 2.59% for trisomy 21 in the maternal age group from 37 to 39 years (Table IV); and 0.78% recurrence rate in the pregnancies with a previous child with Down's syndrome. A total of 1184 pregnancies was monitored with amniocentesis because of advanced maternal age by other laboratories (5, 18, 19, 20). The results of their combined data showed 29 affected cases (2.44%). Without including the data from Wahlstrom et al. (19) due to lack of detailed classification of age, the affected rate in the age group 40 years and over was 3.63% (22 affected cases out of 605 cases studied) (5, 18, 20) and the affected rate in the maternal age group 35 to 39 years was 1.02% (5 affected out of 486 cases studied (5, 18, 20). In a total of 760 pregnancies monitored because of a previous child with Down's syndrome, five affected cases were found (recurrence rate of 0.65%) (5, 17, 19). Thus, our figures of affected cases

TABLE VI

Comparison of the Outcome of 101 Pregnancies with Amniocentesis and 104 Control Pregnancies without Amniocentesis

Outcome	Amniocentesis Pregnancies		Control Pregnancies	
Live	94		100	(1 set of twins)
Apparently normal	90		95	
Birth Defects	2	(1 club foot; 1-ventricular septal defect and coarctation of aorta)	3	(1 club foot; 1 mild thoracid deformity; 1 funny looking facies)
Other problems	2	(1-neonatal myasthenia gravis; 1-cystic fibrosis)	2	(both methadone withdrawal)
Therapeutic abortions	4	(after prenatal Dx.)	0	
Spontaneous abortions	3	(1-amnionitis due to repeated amniocentesis; 1-multiple central nervous system abnormalities, and post amniography amnionitis; 1-fetal death *in utero* due to severe maternal diabetes)	1	(mother developed Hodgkin's disease at 3rd month of pregnancy)
Stillbirth	0		4	

are higher than the frequencies produced by the combined data from the other laboratories.

Problems and pitfalls in prenatal cytogenetic diagnosis have been frequently discussed (10, 12, 15, 21, 22, 23). The finding of polyploidy in amniotic fluid culture is no longer alarming. According to Walker et al. (24), 55% of amniotic fluid cultured cells contained more than 3% polyploid cells. Their study showed no correlation between polyploidy and gestational age, but there appeared to be a correlation between the number of days taken to produce a satisfactory harvest, and a high frequency of polyploid cells.

The problem of verification of a prenatal cytogenetic diagnosis is a real one. Since most of the therapeutic abortions were done by using hypertonic saline instillation, very rarely could we succeed in culturing the macerated fetal tissue for confirmation. It is certainly preferable to use hysterotomy or prostaglandin for abortion so as to yield viable fetal tissue for confirmation. In one reported instance (21), in which prenatal diagnosis of an unbalanced translocation was made from the cultured amniotic fluid cells, the cord blood of the abortus from a hypertonic urea abortion showed a balanced translocation resembling that found in the mother. However, successful tissue culture derived from the placental tissue, showed the same unbalanced translocation as that found in the cultured amniotic fluid cells. Apparently, an admixture of maternal and fetal circulation in the cord blood occurred in this case.

Diagnosis of chromosomal mosaicism is still a difficult problem. In our series, we have made three diagnoses of chromosomal mosaicism. The first case of XO/XY mosaicism showed only 45,XO cells in the first amniotic fluid culture and only 46,XY cells in the second amniotic fluid culture. The possibility of clonal outgrowths from single cells was considered (12). Cytogenetic confirmation of the fetal tissue was not possible because of the hypertonic saline abortion. The fetus was a phenotypic male with no gross abnormality. The case of XO/XX mosaicism was diagnosed from multiple tissue culture flasks from both the first and second amniotic fluid cultures. Again, the fetal tissue could not be successfully cultured due to severe maceration after hypertonic saline abortion and the abortus appeared to be a phenotypically normal female fetus. Nevertheless, the finding of a grossly normal fetus with chromosomal mosaicism in the amniotic fluid cell culture, especially involving sex chromosomes, falls within the possibility of phenotypic spectrum of mosaics. We know that the phenotypic manifestations in individuals with XO/XY mosaicism vary from phenotypic females with clinical Turner's syndrome to "mixed gonadal dysgenesis," to phenotypic males, some with hypospadias and abnormal testes (25). Individuals with XO/XY mosaicism also may vary a great deal clinically with potential short stature and gonadal dysfunction as two of the most frequent features (26), which certainly are not assessable at 20 weeks of gestation. According to Singh and Carr (27), in a fetus with XO chromosomal constitution, ovaries were formed normally in the early gestational period at least from 5 weeks to 4 months but degenerated later in the absence of the second X chromosome. Thus, a fetus with an XO chromosomal constitution may have normal appearing ovaries at 20 weeks of gestation. The third case of mosaicism in our series, 46,XX/47,XX,+20, was found in a 41 year old mother, who had a previous child with Down's syndrome. The extra No. 20 was identified by both Q- and G- banding and recovered from two separate tissue culture flasks. Again, hypertonic saline was used for the abortion, and the fetal tissue failed to grow in tissue culture due to severe maceration. Pathologically, the abortus showed no gross abnormality. Of the two previously reported cases of trisomy 20, one was a 7 month old infant with no gross anomaly but failure to thrive and underdevelopment (28), and the other was a 7 year old girl who had partial trisomy for the short arm of a No. 20. She had only mild mental retardation and a few skeletal abnormalities including spondylar dysplasia, thoracic kyphosis, and hypoplasia of the maxilla (29). Therefore, it is possible that a low grade trisomy 20 mosaicism like our case may appear grossly normal.

It is important to emphasize here again that chromosomal mosaicism should only be diagnosed when the same type of chromosomal abnormality is found in a proportion of cells from multiple independently cultured flasks. In our series, a diagnosis of mosaicism was not considered in 13 cases where either an extra chromosome or a structurally abnormal chromosome was found in a proportion of cells from only one tissue culture flask.

One cytogenetically confirmed case of trisomy 13 mosaicism (46,XX/47,XX,+13) was reported by Bloom et al. (30). This mosaicism was verified by the karyotype analysis of cultured fetal tissue obtained by hysterotomy abortion. The abortus was a well-formed female with no obvious stigmata of trisomy 13 syndrome, but with absent right umbilical artery, right duplication of kidney and fundal notching of the uterus.

Without describing the origin of the abnormal cells from one or multiple tissue culture flasks, we can make no comment on the case reported by Katayama et al. (22) where 46,XX/47,XX,+C was recovered from the primary culture of the amniotic fluid cells and normal 46,XX cells were recovered from an apparently different culture flask in the first passage as well as from the baby who was phenotypically normal.

Cox et al. (31), by examining discrete colonies grown out from amniotic fluid cells, suggested that karyotypes be done from a series of different colonies for less ambiguous interpretation of chromosomal mosaicism.

The possibility of maternal cell contamination is another confusing issue. According to Nadler's experience (4), 0.5% of the cases may be contaminated with maternal cells, but we so far have not to our knowledge experienced this problem. One error in prenatal cytogenetic diagnosis was reported by Katayama et al. (22). In this case, a female infant with Down's syndrome (47,XX,+21) was born after a prenatal diagnosis of 46,XY was made. In the collection reported by Milunsky (5), out of 1633 prenatal diagnoses (including 115 cases for prenatal sex determination and prenatal biochemical diagnosis) the fetal sex was incorrectly diagnosed in 7 cases (0.43%). In all 7, males were born instead of the predicted female infants.

As to the prenatal sex determination in pregnancies at risk for an X-linked disorder, we must emphasize again as we did in 1971 (32) that karyotype analysis of the cultured amniotic fluid cells is the only accurate means.

Determination of X-chromatin and Y fluorescent body in the uncultured amniotic fluid cells is not accurate enough for such a diagnosis. This is well exemplified by the case of 46,XYq- in our series showing no X-chromatin nor Y fluorescent body in the uncultured amniotic fluid cells.

Regarding the problems of carrying a fetus of 47,XXX or 47,XYY it is known that individuals with 47,XXX or 47,XYY are frequently phenotypically normal (33, 34). The presence of three X chromosomes apparently increases the risk of 47,XXX females for mental retardation or mental illness. The magnitude of this risk is not known, but it must be explained to the parents. Although there is evidence for tall stature in XYY males, the presence or frequency of abnormalities such as mental subnormality or mental illness and aggressive behavior has not been completely substantiated. The whole picture must be interpreted with great caution to the parents. In this series, we had one case of double trisomy, i.e., XYY and trisomy 21, where the parents elected to have a therapeutic abortion mainly because of the finding of trisomy 21.

As to the problems of counseling parents who are carrying a fetus with an apparent balanced translocation, it is known that except for balanced centric fusion type of translocations which are associated with normal phenotypes, apparently balanced reciprocal translocations may represent aneusomy by recombination which may lead to multiple congenital abnormalities, as suggested by Lejeune and Berger in 1965 (35). We believe that this risk has to be explained to parents. With various banding techniques, it is possible that one can actually identify aneusomy by recombination. In fact, one such case derived from an inversion was found with the trypsin Giemsa banding technique (36).

In conclusion, prenatal diagnosis has brought a new dimension to the field of medical genetics. With more experience and the various newly developed techniques for chromosome identification, we are looking forward to further exciting achievements in prenatal cytogenetic diagnosis.

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Surgery of Pancreatitis

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All classifications of pancreatitis are based upon personal views of the physician who conceives it. They are also based on factors which are either etiologic, clinical, pathologic, surgical, anatomical, or histologic.

In the medical literature Fitz (4), Opie (10), Lagerlof (8), Joske (7), Howard (6), Sarles (12), Gambill (5), and many others have tried to classify pancreatic disease, but until now a useful classification has never been developed because of failure to achieve a correlation between clinical and pathologic findings in pancreatitis. It may be possible that the development of a skinny needle for pancreatic biopsy, which is in trial now (3), may be the step that will allow the development of a good classification of pancreatic disease.

Meanwhile, as we are most concerned with the adequate treatment of our patients, a very simple classification could be used: a patient with pancreatitis is classified as having acute pancreatitis when he is acutely ill, and as having chronic pancreatitis when otherwise. It may look very simple and unscientific, but in practice it works out very well, because it is simple.

Acute Pancreatitis

As we are practical surgeons, when we face a patient with pancreatitis, the only important factor that may influence our decision on how to treat him should be the answer to a question: is our patient in acute distress? If yes, he should be treated on an intensive care basis, as any patient in such conditions should be. If not, another question should be asked: is our patient in chronic distress that impairs his normal way of living? If yes, we should consider, after admission to a hospital and proper examination, if the cause of his distress is amenable to surgical correction (and this goes for the acutely ill, too). This attitude is proper for any disease and should be strongly urged in pancreatitis, regardless of classifications and technical considerations.

These considerations might give the wrong impression that we should not pay attention to statistics, to review of patients and results of different types of treatment. Those informations should be always considered, but only for the improvement of the particular patient we are treating now, and not for the improvement of the statistics we are most concerned with, at that time.

It is known that, at Mount Sinai Hospital, New York, and at many other medical institutions in the world, the treatment of acute pancreatitis under intensive care in specialized units, has resulted in a consistent drop in mortality for this disease.

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Our patient may need surgery anytime during his treatment, and the exact timing and careful judgment of surgical indication, may be the difference between success and failure.

On our surgical service, we avoid routines for treatment, because we teach our residents that every patient is a particular case and should be treated accordingly, and that means that routine measures that may be helpful to a certain number of patients, could be very harmful to others. But there are signs that should be investigated in every patient to lead us into the most appropriate care for each one of them.

In acute pancreatitis, the proven or strongly suspected presence of biliary lithiasis is an indication for surgery, as soon as the patient's general condition warrants a successful operation, and naturally, this should be performed by a skillful and experienced surgeon.

Also, the evidence of worsening of the disease despite adequate treatment, is another indication for surgery, although, in these cases, the prognosis is generally poor. But we should not deprive our patient from the possibility of treating surgically a potentially curable cause of his pancreatitis.

Drainage of blocked intra- or retroperitoneal collections, performance of biliary drainage, or gastrostomy may improve the patient's chances of recovery, with less discomfort, by removing his nasogastric tube, decompressing his biliary tree, and evacuating toxic material from the peritoneal cavity.

We have had good and bad results from this procedure and have a word of warning about it: it may be very helpful in some instances, but should never be a routine procedure for all cases of acute pancreatitis. A large hospital in Rio de Janeiro obtained a good improvement in mortality rates after the routine use of this type of surgery for acute pancreatitis. It is our opinion that the better results were due to the necessity of intensive care for those surgical patients who were better treated than the nonsurgical ones.

The routine use of surgery in acute pancreatitis will lead to surgery on patients without indications, with an increase in mortality in this particular group, although it may improve the results in surgical cases that otherwise would not be operated upon.

It is an obligation of the surgeon to develop his clinical judgment for a most perfect indication of when to operate on a patient, and this can be obtained only by twice or three times a day and sometimes hourly assistance to the patient with acute pancreatitis.

Without this, he will be forced to follow rules and routines, being unable to choose the best for that man or woman who is expecting from him, not only scholarly knowledge, but special and individual care.

Complications of Acute Pancreatitis

Abscesses and hemorrhage are complications difficult to deal with in acute pancreatitis. They should both be treated surgically as soon as possible, and this is the only chance of survival those patients have. We will not enter into technical considerations of surgery of hemorrhage and infection, because any good textbook of surgery has it well described. But some points should be taken into consideration:

First, purulent collections should be adequately drained and sometimes may need more than one operation for that. It is frequently very difficult to manage the drains, specially if they cannot be placed in a proper dependent position. Dreiling (3) has proposed drainage of those abscesses into the stomach, with an external tube coming out as a gastrostomy, and this, we believe, may be very helpful in the management of retrogastric abscesses.

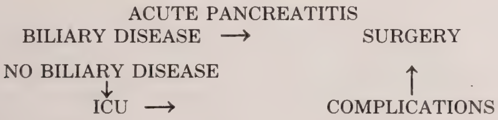
Second, hemorrhage is generally due to erosion of a cyst or an abscess into a major vessel of the upper abdomen. When one is faced with such catastrophic occurrence one must ligate the bleeding vessel, and sometimes this will bring as a consequence the necessity of performing a pancreatic and/or splenic ressection. This may be a very difficult procedure and results are generally poor.

Third, most of the time, hemorrhage results from improper or rough handling of the inner surface of an abscess or cyst, with resulting trauma. Knowing this, a surgeon may prevent unpleasant surprises on the postoperative course of many patients.

Jaundice is not an indication for surgery in acute pancreatitis, unless there is evidence of choledocholithiasis. Jaundice secondary to pancreatic edema subsides under medical management.

Now a word about total pancreatectomy in acute pancreatitis. In our experience, when this operation is technically feasible, the patient does not need it. On the other hand, when the patient might be improved by it, it is technically impossible. So, unless a group of highly experienced surgeons recommends it, after a good clinical trial, it should not be considered as treatment of acute pancreatitis.

To summarize, surgery of acute pancreatitis depends on the existence of surgically correctable lesions that are possibly a cause or a complication of the disease. The indication for surgery should not be hurried or postponed, because proper timing is very important for the adequate surgical management of the disease.



Chronic Pancreatitis

Our patient is not in acute distress, but he has symptoms that do not allow him to enjoy a normal, productive life.

He may complain of pain, diabetes, diarrhea, an abdominal mass, jaundice, ascites, hemorrhage, portal hypertension, biliary cirrhosis, pulmonary tuberculosis, high intestinal obstruction and pancreatic lithiasis, which are the most common complications of chronic pancreatitis.

Portal hypertension is beyond the scope of our presentation, hemorrhage was already briefly considered, diabetes, diarrhea and pulmonary tuberculosis are clinically managed and biliary cirrhosis should not appear if all biliary tract disease is conveniently and properly handled as soon as diagnosed.

Diarrhea may be pancreatic in origin and under the surgical point of view, proper diagnosis should include the possibility of pancreatic tumors. As we are dealing only with pancreatitis, in this case, adequate diet and substitution medication with pancreatic enzymes, generally control this complication.

Biliary Disease

With the wider indications for surgery in biliary diseases, the incidence of pancreatitis as a serious complications of gallbladder and common duct stones is probably decreasing. Our main concern is now directed to alcoholic pancreatitis which leads to complications such as jaundice, cysts, abscesses, pancreatic lithiasis, high intestinal obstruction, ascites and intractable pain.

When jaundice is secondary to biliary lithiasis and there is associated pancreatitis, the adequate treatment of biliary disease will solve the problem in the majority of cases. So, jaundice associated with pancreatitis can be due to: 1) common duct stones; 2) pancreatic fibrosis; 3) compression of the common duct by cysts or abscesses and 4) pancreatic edema. All, except the last, are amenable to surgical correction. Edema, as we have pointed out when dealing with acute pancreatitis, may subside under medical management, and is not, per se, an indication for surgery.

Jaundice is a surgical complication of alcoholic chronic pancreatitis. The biliary obstruction of pancreatic fibrosis needs decompression that is better achieved by choledocho-duodenostomy or choledocho-enterostomy by a Roux-en-Y procedure. There is much discussion on which type of anastomosis is preferable. We use a side-to-side choledocho-duodenostomy with very good results, specially in aged patients because of the simplicity of its performance. Whenever there is necessity of complete diversion of the bile flow from the duodenum, we prefer cutting across the common duct and anastomosing it to a defunctionalized loop of bowel (Roux-en-Y).

Pancreatic Cyst and Ascites

Pancreatic cysts should be drained in the simplest possible way, preferably internally to a hollow viscus. The stomach, jejunum or duodenum can be used, according to the anatomical situation of the cyst, and only if its walls are thick enough to take a good suture. Infection is also a contraindication for an anastomosis, except for infected cysts or abscesses situated behind the stomach, in which case, the wall of the abscess is contiguous to the posterior gastric wall, through which the drainage is made.

Knowledge of these principles and great care in handling the inner walls of the cyst will give a good postoperative course with low mortality. This means that external drainage should be used in all other occasions. We have had good results from this procedure. The incidence of fistulas is low and they generally close under medical management in between a few days and three months of treatment. When a fistula does not close, it can be excised and the duct or cavity from which it originates should be anastomosed to a loop of jejunum.

Pancreatic ascites has been associated with perforated pancreatic cysts, in our experience. Machado et al (9) and Cameron et al (2) have had also the same observation. The adequate treatment of the cyst or the performance of a pancreato-jejunal anastomosis when there is an opening in the main pancreatic duct will conveniently treat the ascites associated with pancreatitis.

Another very serious conditions that should be mentioned, is the rupture of a cyst into the free peritoneal cavity or into an adjacent viscus such as the stomach or the colon. Rupture into the peritoneal cavity may cause severe peritonitis if there is associated infection and our mortality in treatment of pancreatic cysts has been associated with such complication that sometimes cause subphrenic abscesses or difficult-to-control hemorrhage.

When hemorrhage is not catastrophic, rupture into the stomach will eventually lead to cure of the cyst, acting as an internal drainage operation. Rupture into the colon will always need laparotomy and adequate external drainage because of contamination and possibility of abscess formation.

It should never be forgotten that all cysts must be carefully inspected and biopsied, to avoid internal drainage of a neoplastic cyst. Malignant cysts must be always resected, with associated pancreatectomy.

Pancreatic Calcifications

Pancreatic calcifications are sometimes the clue to diagnosis of pancreatitis. They are usually associated with alcoholic or familial pancreatitis. Calcifications are not an indication for surgery but, as was pointed out by Bartholomew (1) in 1958 and corroborated at Mount Sinai Hospital (11) in 1960, they may be associated with pancreatic cancer.

Patients with pancreatic calcifications should be operated upon whenever there are symptoms that could be related to pancreatic inflammation or tumor. Otherwise, pure pancreatic calcification without association with pain or any other complication, is not an indication for surgery, but only for careful follow-up.

High Intestinal Obstruction

Usually associated with enlargement of the pancreas and compression of the superior mesenteric vessels over the third portion of the duodenum. We have had the opportunity of performing a few duodenal-jejunal anastomoses on patients with such complication. This operation is sometimes indicated in chronic pancreatitis with fibrotic enlargement of the pancreas, in cases in which one does not consider pancreatectomy the best procedure. It is not indicated in acute pancreatitis when the obstruction is due to edema of the head of the pancreas that subsides after adequate treatment of the disease. Eventually, a feeding jejunostomy may help maintain nutrition while the edema subsides.

Intractable Pain

We believe that pain is intractable when the patient has repeated attacks or persistent abdominal and dorsal pain that impairs his normal way of living. We have had the opportunity of admitting patients to the hospital for surgery of pancreatic pain, who, after a few days of diet, intravenous fluids, blood transfusions and sometimes psychiatric assistance, have improved so much that they were discharged without surgery. This pain is mostly seen in alcoholics and the main difficulty in handling such patients is that they do not stop drinking.

Psychiatric consultation is mandatory in most of these cases, and also social evaluation of the patient, specially if he may need extensive pancreatic ressection that will indicate insulin and pancreatic enzymes substitution therapy. In our country, due to the higher incidence of pancreatitis in the poor population, we consider carefully the indications for pancreatic ressections because of the difficulty of maintenance of such patients after operation.

In our experience, good results in treatment of pain in chronic pancreatitis, either medical or surgical, is directly related to the abstinence of alcohol. All our patients operated upon for chronic pancreatitis had good results if they stopped drinking, and bad results, needing sometimes repeated operative procedures, if they persisted in the alcoholic habit.

Since pancreatitis is a benign disease, we try to avoid extensive pancreatic ressections as a primary procedure, using drainage operations whenever indicated. The most important consideration is the existence or absence of pancreatic ductal enlargements and stenoses.

Whenever there is ductal ectasis, pancreato-jejunal anastomosis should be considered as the procedure of choice, avoiding pancreatic ressection. On the other hand, extensive fibrosis and destruction of the gland indicate caudal pancreatic ressection, and lately we have been associating it with a Puestow type of anastomosis to the remaining portion of the gland, specially if there is concomitance of fibrosis with ductal enlargement.

Pancreato-duodenectomy is indicated when the head of the pancreas is completely substituted by fibrotic tissue and calcification and should be done only if careful evaluation of the patient and intraoperative examination warrants that it is the only adequate treatment.

In the last ten years, we have taken personal care of some two hundred patients with pancreatitis and only one pancreato-duodenal resection was performed for this disease. Also, only five caudal pancreatectomies were done, and ten Puestow procedures.

The evaluation of a patient with pancreatitis is easier and more complete today, due to the existence of endoscopic pancreatocholangiography. This wonderful examination provides the surgeon with information that used to be available only at the operating room. Although modern medicine provides us today with echograms, CAT scans, endoscopy, and radioactive isotopes, a good doctor must always remember that time spent talking to a patient and examining him carefully is the best way of giving him better care and better treatment.

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Studies on Melanocytes

IV. Melanocytes in Extraocular and Orbicularis Muscles

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Abstract

Melanocytes were found in the extraocular and orbicularis muscles and also in the episcleral and retrobulbar areolar tissue of human fetuses 12–18 weeks of gestation. They were a constant finding in the fetal orbit, but were uniformly absent in adults of both races, a finding parallel to that in the muscles of mastication and contrary to that of nasal and laryngeal mucosa where melanocytic colonization occurs in postnatal life. This may explain the relative prevalence of primary melanomas in the nasal cavity and larynx and their great rarity in the orbit. The pertinent world literature is tabulated.

Introduction

The presence of melanocytes is recognized in the epidermis, cutis, in certain mucous membranes (1, 2), leptomeninges, and within the inner ear (3), and the eye. However, their regular occurrence within striated muscle and the dental primordium has only recently been documented by us in man (4, 5). While Boyd (6) occasionally observed argentaffin premelanocytes in the connective tissue of the orbit of human embryos, to our knowledge melanocytes have not been previously described within the extraocular muscles apart from cases of oculodermal melanosis (Nevus of Ota).

Materials and Methods

The heads of twelve human fetuses (nine Caucasian and three Negro), 10–18 weeks of gestation, were formalin fixed, embedded in paraffin, and sectioned in a frontal plane. Multiple step sections through the orbits were stained by the Masson-Fontana method for melanin. The levator palpebrae superioris muscle was removed at autopsy from 5 neonates (all Caucasian), a five-year-old child (Negro) and 7 adults (one Negro). This material likewise was formalin fixed and paraffin embedded, but stained with a modified Warthin-Starry technique (7) which is more specific for melanin than the Masson-Fontana method and thus does not stain the age-dependent lipofuscin of the muscle fiber.

Results

Melanocytes were found in the extraocular muscles in all fetal cases except the youngest (10 weeks). They appeared as ovoid cells with short processes (Fig. 1, 2) or bipolar structures filled with brown to black granular pigment

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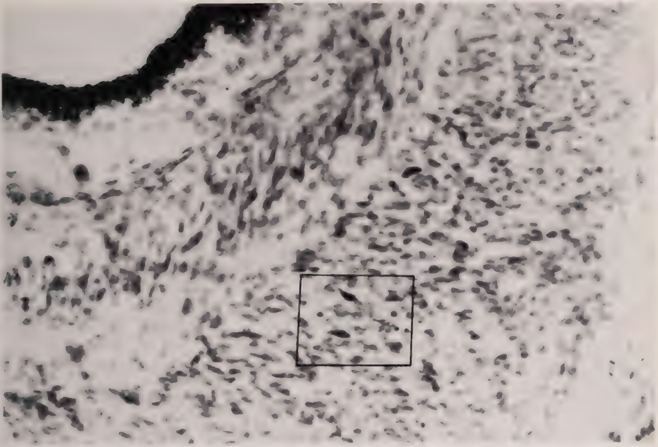

FIG. 1. Melanocytes within extraocular muscle (boxed-in area). Note pigmented retinal layer in left upper corner (Masson-Fontana, reduced from × 125).

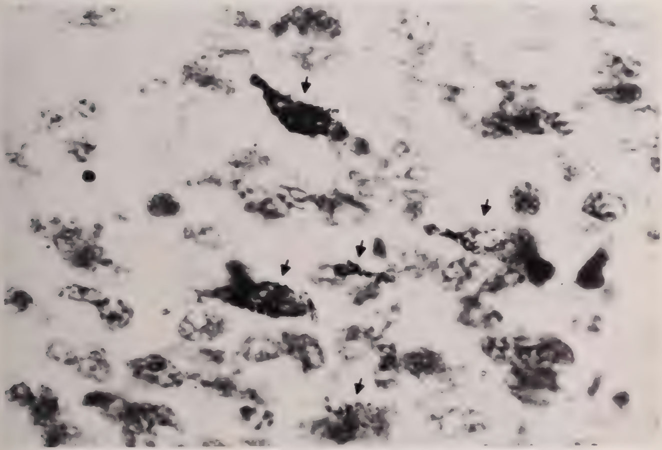

FIG. 2. Corresponds to boxed-in area of Figure 1. There are five melanocytes in this field (arrows) some of which show a negative nuclear image (Masson-Fontana, reduced from × 950).

TABLE I

Primary Orbital Melanomas

Author	Sex & Age	Symptom	Location	Treatment	Follow-Up
Walter (1893)	F-48	Proptosis—6 years	Within muscle cone	Orbital Exenteration	
Benedict (1941 & 1966)	M-14	Proptosis-6 years Oculodermal melanosis (Nevus of Ota)	Retrobulbar	Orbital Exenteration Residual tumor at apex and fissure	Free of disease—20 years
Rottino and Kelly (1942)	M-27	Proptosis—5 years	Filling entire orbit	Orbital Exenteration, Radiotherapy	Alive with tumor—2 years
Foster (1944)	F-65	Proptosis, pain paresis of inferior rectus muscle—2 months	Lateral to lateral rectus muscle	Excision	Free of disease—22 months
Bonnet (1951)	M-adult	Mild proptosis followed by subjective complaints for 4 years with decreased vision and pain. Both of which improved with radiotherapy given for retinal detachment 2 years later. Loss of vision the next year "absolute glaucoma" with protrusion.	Retrobulbar, surrounding optic nerve	Orbital Exenteration	
Offret (1951)	F-52	Painful proptosis with palpebral and subconjunctival hemorrhage	Palpable mass in inferior temporal quadrant anteriorly	Local excision	Rapid recurrence with invasion of parts of face, muscles of mastication and pharynx. Lost to follow-up but presumed dead of disease.
Cardia (1961)	F-57	Swelling above infraorbital rim—2 years	Anterior orbit, inferiorly	Excision	Dead of metastatic disease—6 months
Rank (1963)	F-11	Congenital oculodermal melanosis (Nevus of Ota) with puffy lids, proptosis and blindness	"Dense pigmentation of deep tissues" and orbital periosteum	Orbital Exenteration	Alive and well—6 years

Verdaguer (1965) Reese (1974)	F-12	Melanosis of lid, sclera and iris Proptosis—1 year Papilledema	Inferior temporal quadrant	Orbital Exenteration	Orbital recurrence. Dead of tumor
Jay (1965)	F-64	Proptosis—1 year Oculodermal melanosis (Nevus of Ota)	Retrobulbar, above optic nerve	Orbital Exenteration	Dead of metastatic disease—10 months
Tjanidis et al. (1966)	F-15	Oculodermal melanosis (Nevus of Ota) and angiomatosis. Progressive from birth. Increasing painful proptosis.		Tumor of temporal skin reported as malignant melanoma	Patient refused orbital exenteration, became cachectic and developed a large liver (probably metastatic) and died with symptoms of intracranial hypertension.
Hagler and Brown (1966)	M-57	Proptosis—3 years Oculodermal melanosis (Nevus of Ota)	Within orbital apex	Orbital Exenteration Residual tumor at apex	Free of disease—6 years. (This case is considered to be a cellular blue nevus by Speakman and Phillips)
Wolter et al. (1966) (1971)	F-63	Proptosis Partial visual loss—4 weeks subconjunctival tumor	Adjacent to sclera and optic nerve Inferior to lateral rectus muscle	Orbital Exenteration	Free of disease—7 years.
Henderson (1972)	M-13	Upward displacement of eye Proptosis—1 month	Inferior temporal quadrant	Simple excision of encapsulated lesion	Free of tumor—13 years.
Henderson (1972)	M-49	Proptosis—1 month	Posterior superior temporal quadrant	Biopsy	Local recurrence and intracranial extension. Dead of tumor—2 years.
Speakman and Phillips (1973)	M-61	Oculodermal melanosis (Nevus of Ota). History extending over 11 years with recurrent episodes of right proptosis, blurred vision, chemosis and hemiparesthesia of right lower face. During the last such episode there was sudden total and irreversible loss of vision. X-ray showed defect in orbital floor and mucosal thickening of antrum.	Retrobulbar	Exploration and biopsy	Alive and well—32 months. (Considered to be cellular blue nevus)

TABLE I *continued*

Author	Sex & Age	Symptom	Location	Treatment	Follow Up
Speakman and Phillips (1973)	F-29	Oculodermal melanosis (Nevus of Ota). First noted bluish spots of periorbital skin at age 11. These spread to right forehead, cheek and side of nose. At age 29 proptosis and diplopia.	Retrobulbar	Partial exenteration including orbital floor	Died of disease—2 years later
Jakobiec et al. (1974)	F-42	Oculodermal melanosis (Nevus of Ota). Diplopia of several weeks. Palpable mass below supraorbital rim.	Anterior—Superior to globe	Orbital exenteration Resection of supraorbital rim and floor of frontal sinus	
Drews (1975)	M-75	Mass in anterior orbit	Extending to apex	Local excision	Recurrence at 6 weeks followed by central retinal artery occlusion, invasion of sinus, abnormal liver scan and bleeding from tumor. Death from stroke

Note: A right orbital melanoma was removed by Dr. Coppetto of the University of Conneticut in November of 1976. The patient, a white woman, aged 49 years, had decreased vision for a year and a half and proptosis of one year's duration. This lesion was presented at a pathologists' meeting by Dr. Ivan Damjanov to whom we are indebted for this information.

and frequently showing a negative nuclear image. They generally occurred as scattered cells between individual muscle fibers. Occasionally, they were seen in the loose areolar retrobulbar tissues and in or outside the sclera. Melanocytes were found in some of the extraocular muscles in all specimens and on two occasions in the orbicularis oculi muscle.

Melanocytes were found in two out of five neonates and in the five-year-old child. None were present in the adult material.

Discussion

Primary malignant melanomas develop wherever melanocytes occur. The conjunctiva, cornea, iris, ciliary body and choroid are typical sites of origin within the eye. Scattered melanocytes occur in the optic nerve and sclera mainly along penetrating vessels and nerves, and also along the optic nerve sheath (8). Consequently, melanomas or melanocytomas have been observed in the optic disc, in the sclera and along the optic nerve (8). The majority of orbital melanomas are secondary, with escape of the neoplasm from the eye or spread from an adjacent structure such as the eyelid, epibulbar area, paranasal sinuses or meninges, or metastatic from an intraocular or distant source (9).

Primary orbital melanomas are exceedingly rare with only five cases accepted by Henderson (10) up to 1972. A pertinent clinical photograph and a picture of a gross specimen are shown by Duke-Elder (11). The literature expanded and updated is seen in Table I. Henderson (10) was also unsuccessful in finding an original investigative work which established the existence of melanocytes within the orbit. Reese (8) states that uveal melanocytes normally extend partially through the sclera along emissary vessels, however, in highly pigmented individuals, they may appear at the outer scleral surface and even in the orbital structures. Reese (12) found melanocytes in the extraocular muscles in a case of melanosis oculi. Jay (13) recorded their presence in the orbicularis and temporalis muscles in a case of oculodermal melanosis (Nevus of Ota). Hagler and Brown (14) likewise saw these cells in the orbicularis muscle in the same entity. Henderson and Farrow (9) speculated that primary orbital melanomas may arise from ectopic pigmented foci in the orbit.

Conclusion

Our study has shown that melanocytes occur regularly as a normal constituent of the fetal human orbit and frequently in neonates. There they may be found in the retrobulbar or episcleral loose areolar tissue, typically within the extraocular muscles and occasionally in the orbicularis oculi muscle. In a previous publication, we described the constant presence of these cells in the muscles of mastication of the same type of material (4) as outlined in material and methods.

In tabulating the motor innervation of muscles in which we observed melanocytes, it becomes evident that the cranial nerves III to VII but not IX to XII are involved. In order to strengthen this impression, transverse sections through the neck at 3 levels of 6 additional fetuses were studied. Intramuscular melanocytes were not observed in the muscles innervated by the last 4 cranial nerves or in those supplied by cervical spinal nerves.

The presence of melanocytes in extraocular muscles in the fetal neonatal and childhood material and their universal absence in adults of both races (excepting Ota's nevus) contrasts sharply with laryngeal and nasal mucosal melanocytes which we found to be common in adults but absent before puberty (1, 2). This may explain the relative prevalence of primary melanomas in the nasal cavity and larynx and their great rarity in the orbit.

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Urethral Fascial Sling Operation for Repair of Urinary Stress Incontinence: Ten Cases at The Mount Sinai Hospital from 1972–1973

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Abstract

The aim of this study is to report a series of ten women with urinary stress incontinence who were successfully treated with a urethral sling operation. Although it is clear that properly studied cases of urinary stress incontinence are best repaired by primary or secondary Marshall Marchetti Krantz operation and/or anterior-posterior colporrhaphy with Kelly plication, the sling procedure can offer good results as a tertiary repair. The procedure is technically simple to master by many different surgeons and our sling procedures have provided relief for women who otherwise were incapacitated by their recurrent urinary stress incontinence.

Introduction

This is a report of 10 women with urinary stress incontinence having recurred after a primary repair. The current procedure employs a strip of the rectus abdominis fascia as a sling, in the modified Goebell Frangenheim Stoeckel Aldridge Studdiford fashion. The operative repair is technically simple and reproducibly good results have been achieved in the hands of several surgeons.

A common problem faced by the gynecologist is that of urinary stress incontinence in the female (1, 2, 3, 4). Once the anatomical lesion is verified, an effective mode of repair can be chosen. Primary repair, utilizing anterior colporrhaphy, Kelly plication urethroplasty with or without a posterior repair with or without Marshall Marchetti Krantz operation (5), or Marshall Marchetti Krantz operation by itself when properly selected, has a greater than 80% chance of permanent success.

When tertiary repair is necessary we have found the urethral sling procedure, modified Goebell Frangenheim Stoeckel Aldridge Studdiford operation, a highly efficient operative repair.

Materials and Methods

During 1972 and 1973, 10 patients underwent fascial sling repairs for urinary stress incontinence. Nine out of the ten were after failure of primary and/or secondary repairs. All had progressive urinary stress incontinence for greater than one year prior to present surgery. All were incapacitated by their current urinary stress incontinence to the degree that they needed to wear sanitary

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napkins or diapers to stay dry. None had previously had sling procedures as per Table 1. The patients varied in age from 32 to 51 with a mean of 43.5 years. Their parity varied from 0 to 7 with a mean of 4.1 (figures 1 & 2; Table II).

Of the 10 patients, 5 were without any concurrent diseases. Four of the patients were under chronic medical care for asthma, 2 for diabetes, 2 were obese, and 1 had severe arthritis of the cervical spine.

All of the operations were performed on the teaching service by several different operators with equally good results. After preoperative evaluation including normal cystoscopy, cystometric examination, urine culture and sensitivity and other studies as indicated, the procedure followed was the modified Goebell Frangenheim Stoeckel Aldridge Studdiford operation (6). Identification and adequate mobilization of the para-urethral tissue is necessary to allow the sling to support the urethra properly. Abdominally the approach is via a Pfannenstiel skin incision carried to the level of the rectus fascia. A strip of fascia approximately 20 centimeters long and 2 centimeters wide is isolated

TABLE I

Patient	Sequence of previous surgical procedures
C. D.	1. 1963 anterior-posterior colporrhaphy
	2. 1968 Marshall-Marchetti-Krantz
	3. 1972 sling procedure
L. J.	1. 1966 abdominal tubal ligation and anterior-posterior repair
	2. 1969 anterior-posterior repair with Kelly plication and Marshall-Marchetti-Krantz
	3. 1973 sling procedure
R. M.	1. 1963 vaginal hysterectomy and anterior-posterior repair
	2. 1966 Marshall-Marchetti-Krantz
	3. 1972 sling procedure
J. V.	1. 1960 total abdominal hysterectomy
	2. 1972 sling procedure
L. C.	1. 1960 umbilical hernia repair
	2. 1961 anterior-posterior colporrhaphy
	3. 1966 cesarean section and abdominal tubal ligation
	4. 1972 sling procedure
	5. 1975 total abdominal hysterectomy for fibroid uterus (no urinary stress incontinence before or after 1975 surgery)
L. L.	1. 1970 total abdominal hysterectomy and Marshall-Marchetti-Krantz
	2. 1972 sling procedure
M. C.	1. 1965 anterior-posterior colporrhaphy
	2. 1970 Marshall-Marchetti-Krantz
	3. 1971 total abdominal hysterectomy and bilateral salpingoophorectomy
	4. 1972 sling procedure
L.C.	1. 1967 anterior-posterior colporrhaphy
	2. 1968 total abdominal hysterectomy and Marshall-Marchetti-Krantz
	3. 1972 sling procedure
B. R.	1. 1970 total abdominal hysterectomy and Marshall-Marchetti-Krantz
	2. 1971 anterior-posterior colporrhaphy
	3. 1972 sling procedure
A. C.	1. 1951 anterior-posterior colporrhaphy
	2. 1952 cesarean section x2 because of previous repair
	3. 1972 sling procedure

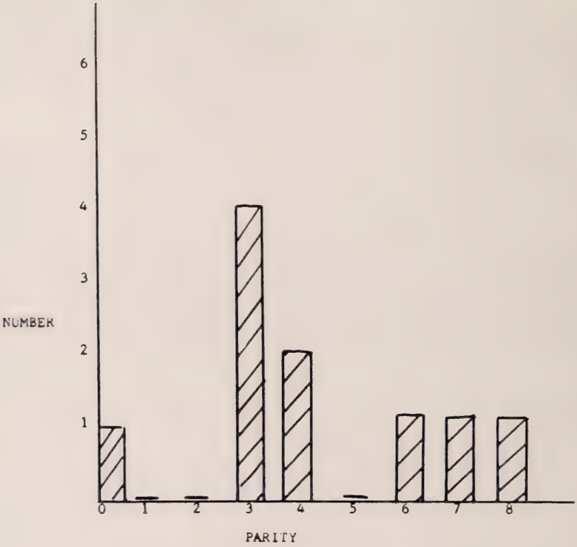

Fig. 1. Parity distribution of patients

and the space of Retzius entered. With the combined abdominal and the vaginal approach, the posterior urethrovesical angle is identified and with sharp and blunt dissection, the fascial strip is fed para-urethrally to effect the urethral sling, and the abdominal ends are fixed to the external oblique fascia with number 2-0 silk sutures. Care is taken at this point to adjust the tension properly. Drains are placed in the space of Retzius (figure 3).

Half of the patients had epidural anesthesia and the other five were intubated and had inhalation anesthesia. Both groups tolerated their anesthesia very well and provided no problems from an operative point of view.

Discussion and Results

In 1972 and 1973, 10 patients at the Mount Sinai Medical Center had fascial sling procedures performed, either as primary, secondary or tertiary repair of urinary stress incontinence. The results 3 and 4 years after the sling procedures have been uniformly good. The procedure has little morbidity. In our small series we had no anesthetic problems, no hemorrhage, no fistulae. There were two cases with superficial wound infections and bacteriuria in all cases. Delay in spontaneous voiding after surgery was the only significant postoperative problem, but all overcame this within one to six weeks.

These 10 women had previously undergone a total of 12 operative repairs with brief successful results. Careful preoperative evaluation is necessary to assure the appropriateness of the operative repair (7). Complete history and physical examination is of the essence since multiple previous surgical procedures can make dissection and lysis of adhesions treacherous. Entry of the bladder at the site of previous adhesions is not uncommon.

Sling tension must be carefully adjusted (8) since anesthetic relaxation may alter the end result. The fascial sling is particularly useful when the quality of the supporting tissue used for the repair is poor. The urethral sling procedure requires similar incisions as would be necessary to repair Green type I and II defects with a combined Marshall Marchetti Krantz procedure and anterior colporrhaphy with Kelly plication (9).

Most authors agree that primary repair of urinary stress incontinence with Marshall Marchetti Krantz operation or anterior-posterior colporrhaphy provides 80 to 90% success (10). It is therefore probably worthwhile to choose one

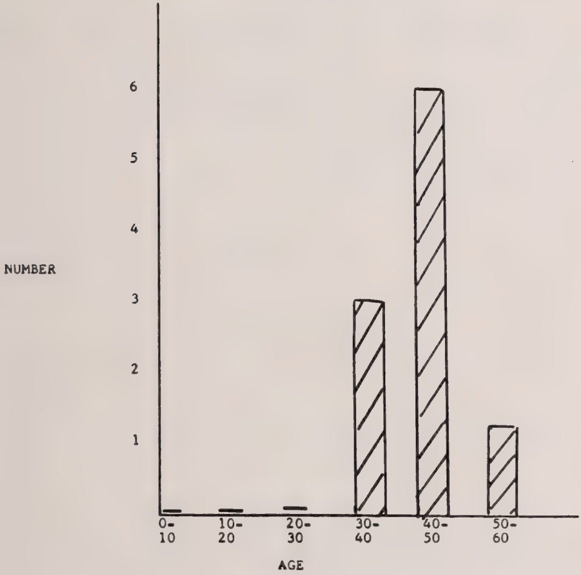

Fig. 2. Age distribution of patients

TABLE II

Distribution of Age and Parity

Patient	Age	Parity
C. D.	47	7146
L. J.	48	4054
R. M.	51	8077
J. V.	49	4024
L. C.	38	3003
L. L.	32	3033
M. C.	46	0000
L. C.	47	6016
B. R.	33	3003
A. C.	44	3023

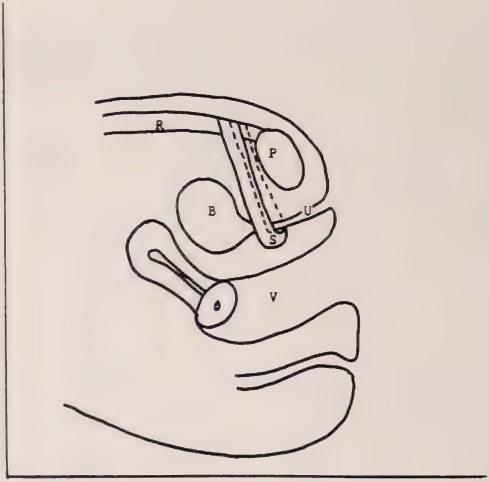

Fig.3. Fascial Sling Procedure-lateral view.

B=bladder,P= pubic symphysis,R=rectus sheath,
S= fascial sling,U=urethra,V=vagina.

of the former procedures for primary repair since they are technically simple procedures and yield such good results. However once recurrence exists, the fascial sling procedure can be employed with little hesitancy. Indeed some authors feel that the sling has a role in primary repair of urinary stress incontinence (10). We employed it as a primary procedure for correction of urinary stress incontinence in one patient who had previously undergone a total abdominal hysterectomy for fibroid uterus and at the time of her preoperative examination she had markedly attenuated supporting tissue with which to work. The aim of the various operative procedures is to reestablish normal anatomical structures and relationships (2, 11, 12). It is gratifying to have the sling repair, particularly as a tertiary procedure, to offer relief to the many women who continue to suffer from incapacitating urinary stress incontinence.

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Granulomatous Vasculitis of the Upper Gastrointestinal Tract: A Case Report

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Abstract

A 25-year-old woman presented with a 4-month history of abdominal pain, nausea, vomiting and weight loss. Gastrointestinal x-ray revealed a marked thickening and irregularity of the folds of the stomach and duodenum. Gastroscopy revealed extensive erosions in the duodenum and stomach. Laparotomy revealed a thickened stomach, enlarged lymph nodes and nodules in the liver. Pathologic examination revealed a vasculitis with granuloma formation affecting primarily the small muscular arteries in the submucosa of the stomach, and the mesentery adjacent to lymph nodes. There was neither peripheral eosinophilia nor eosinophilic infiltration of the lesions. The lungs and kidney were not involved. Necrotizing granulomas not in relation to blood vessels were also found in the liver. With steroid therapy, a clinical remission occurred. We have been unable to find a report of a similar case.

Introduction

Granulomatous vasculitis has been described in association with several clinical syndromes which have features in common and in which there is significant overlap. Allergic granulomatosis, referred to as the Churg-Strauss syndrome, consists of severe asthma, fever, and hypereosinophilia, together with evidence of vascular compromise in many organs most frequently the heart (1). The anatomic changes consist of widespread necrotizing vascular lesions in all stages as seen in periarteritis nodosa, and also widespread extravascular granulomatous nodules associated with, or replacing foci of inflammatory exudate. Although gastrointestinal tract involvement was not conspicuous in the original description, extensive gastric involvement has been subsequently described in one case (2). Loeffler's syndrome has many features in common with the Churg-Strauss syndrome and may be a variant; gastric involvement has also been reported (3). Wegener's granulomatosis is characterized by the triad of necrotizing granulomatosis of the upper and lower respiratory tract, glomerulitis, and widespread necrotizing vasculitis of small vessels (4). Lethal midline granuloma may be a variant of Wegener's granulomatosis (5). Temporal arteritis involves primarily the cranial arteries (6). In these latter three syndromes gastrointestinal involvement is minimal or absent.

A patient presented to us with severe granulomatous vasculitis and granuloma formation limited to the stomach, duodenum, liver and mesentery adjacent to lymph nodes, and without respiratory or renal involvement. There was

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neither peripheral eosinophilia nor extensive eosinophilic infiltration of the lesions. We have been unable to find a report of a similar case; it does not readily fit into any of the established entities.

Case Report

A 25-year-old white woman was admitted to the hospital in November 1975 with the complaint of epigastric pain for 4 months. She was well until July 1975 when she developed mid-epigastric, nonradiating, intermittent pain unrelated to position, food, or time of day. Pain was associated with nausea and vomiting. She also has low grade fever in the range of 37.8–38.3°C. At another hospital multiple duodenal ulcers were diagnosed, but intensive therapy for ulcers produced only slight and temporary improvement. After intensive investigation at another hospital which was inconclusive, the patient was placed on several courses of antibiotics with questionable temporary relief, but without lasting effect. During the week prior to admission, she described increasing abdominal pain, stabbing in character, unrelieved by food or antacids, associated with nausea, and diarrhea. She denied melena, hematemesis, jaundice, or dysphagia. A 27 lb. weight loss had occurred over a 5-month period. A Caesarian section had been performed 8 months prior to admission. The patient denied the use of illicit drug, alcohol, aspirin, or other medication. There was no other significant past history.

Physical examination disclosed a poorly nourished, well-developed woman with moderate distress. The temperature was 38.0°C. The pulse was 104, and the blood pressure was 100/60 mmHg. Abdominal examination revealed moderate mid-epigastric tenderness with mild rigidity, but no rebound or distention. Neither liver, spleen nor masses were palpated. Bowel sounds were normal.

Urinalysis was normal on multiple occasions. The hematocrit was 36.4 percent. The white cell count was 7,200 with 12 percent band forms, 47 percent neutrophiles, 32 percent lymphocytes, 8 percent monocytes and 1 percent eosinophiles. Alkaline phosphatase was 120 milliunits per ml (upper limit 85 milliunits per ml). Serum bilirubin was 0.2 mg per 100 ml. Serum amylase and lipase were normal. Serum iron was 16 μg per 100 ml, and TIBC was 210 μg per 100 ml. There was no occult blood in the stool. Latex fixation, LE preparation, and anti-nuclear antibody were negative on three occasions. Serum gastrin level was normal. Heterophile antibody, C-reactive protein, cold agglutinins, were not present. Gastric analysis revealed normal basal and augmented acidity. Multiple blood cultures revealed no growth. Stool culture was negative for pathogens. Total protein was 6.7 gms per 100 ml. Serum protein electrophoresis showed albumin 39.8 percent, alpha$_1$ globulin 8.6 percent, alpha$_2$ globulin 19.4 percent, beta globulin 16.2 percent, and gamma globulin 16.0 percent. IGG was 625 mg per 100 ml (normal 700–1500). IGM was 186 mg per 100 ml (normal 25–170). IGA and IGE were normal. Records from the previous hospitalizations were reviewed. Electrocardiogram revealed sinus tachycardia. Stool for ova and parasites was negative.

A chest roentgenogram was normal. An upper gastrointestinal series showed thickening and irregularity of the folds of the stomach most marked in the distal body and antrum, and similar involvement of the 1st and 2nd portion of the duodenum (Fig. 1). Barium enema was normal. A liver and spleen scan displayed patchy uptake without discrete mass or filling defect. Bone marrow aspirate was normal except for decreased iron stores.

Upper gastrointestinal endoscopy revealed multiple punctate, isolated, superficial erosions in the stomach, each of which was surrounded by an erythematous border. In the duodenum there was extensive confluent superficial erosion involving most of the mucosa. Endoscopic biopsy was reported as showing acute and chronic inflammatory disease. At laparoscopy multiple small white plaques were seen on the surface of the liver. Liver biopsy performed at the time of laparoscopy revealed nonspecific reactive hepatitis.

Because of the persistence of fever, abdominal pain and nausea, and because of the possibility of lymphoma being present, laparotomy was performed. The stomach wall appeared thickened, but the serosa was smooth and normal. Several firm nodules were felt in both lobes of the liver. Prominent firm lymph nodes were found in the omentum and mesentery. Biopsies of a liver nodule, mesenteric lymph nodes and a full thickness biopsy of the gastric wall were performed.

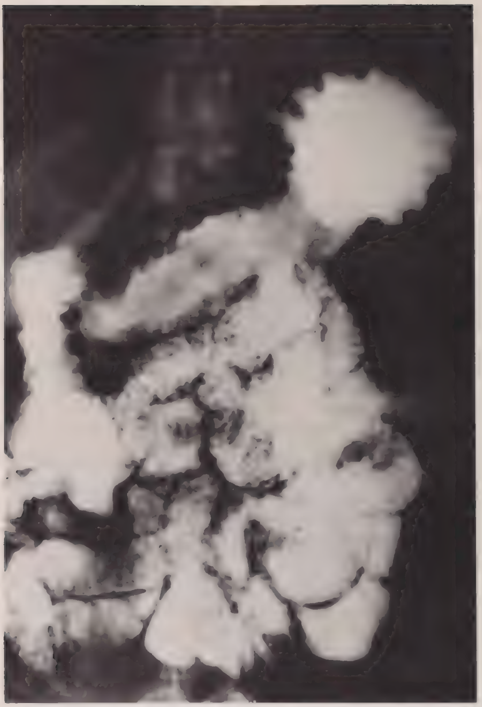

FIG. 1. Upper gastrointestinal X-ray showing thickening and irregularity of the folds of the stomach and proximal duodenum.

Pathology

The lesions in the gastric wall and those in the mesentery were similar. In both instances, small muscular arteries up to 1 mm in diameter and small venules exhibited segmental lesions, but were still clearly recognizable (Fig. 2). The lumina in these segments were occluded by thrombi containing abundant leukocytic cellular debris. Foreign body type giant cells were prominent, especially at the level of the elastic lamina, which was split and fragmented. Contiguous segments of the diseased arteries, as well as adjacent vessels were totally spared by the inflammatory process. A few smaller arteries were occluded by partly recanalized thrombi without any inflammatory reaction or destruction of their walls. In the stomach these vascular changes were entirely limited to the submucosa. In the mesentery the lesions were in the proximity of the hilum of lymph nodes. The lymph nodes themselves contained no vascular lesions and their architecture was normal.

Smaller granulomata composed of collections of histiocytes with a few multinucleated cells and a sprinkling of lymphocytes and plasma cells, but without necrosis, were present in the submucosa

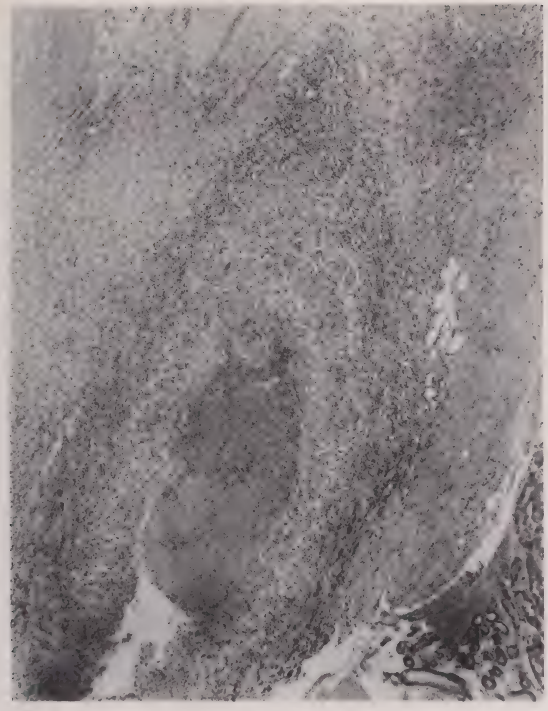

FIG. 2. Small gastric artery. Numerous histiocytes and some small multinucleated cells are present in the wall. A thrombus occludes the lumen. H & E stain (× 40).

and lamina propria. (Fig. 3). In some instances, these granulomata were located in the immediate vicinity of capillaries. The other layers of the wall of the stomach were totally free of such lesions, inflammatory infiltrates of any kind or any other morphological abnormalities.

The nodular lesion of the liver measured approximately 5 mm in diameter and consisted of a well defined subcapsular area of necrosis with fibrosis of the surrounding parenchyma. The central portion of the lesion was composed of a mass of necrotic cellular debris. Surrounding this area of necrosis, there was a zone of fibrous tissue and inflammatory cellular infiltrate. A definite predominance of histiocytes with few small multinucleated cells and fibroblasts was evident. It was most cellular towards the center, and there was gradual transformation into denser collagenized fibrous tissue peripherally. The cellular infiltrate was heavier in the outer laters of the lesion, and its main component was lymphocytic and plasmocytic with less than ten percent of polymorphonuclear leukocytes. Among these, eosinophiles predominated slightly over neutrophiles, but were not conspicuous. No traces of a blood vessel wall were recognizable in these foci. The fibrosis extended into the neighboring hepatic lobules, preferentially encompassing the portal areas.

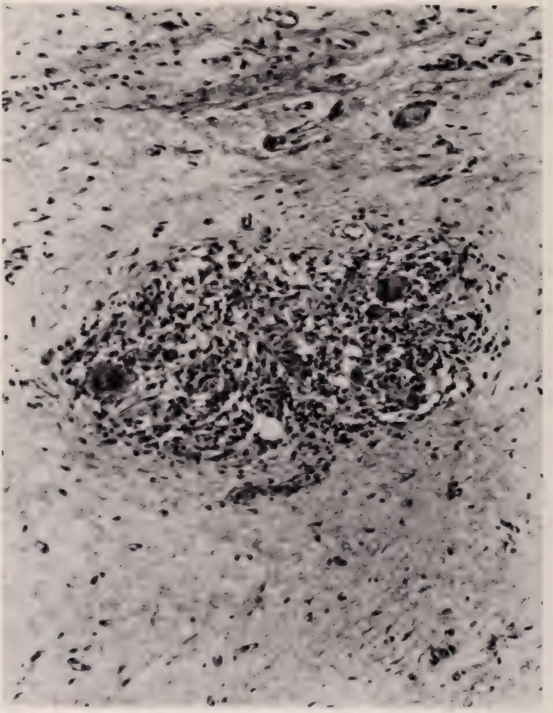

FIG 3. Small nonnecrotizing granuloma in submucosa of stomach. H & E stain (× 100).

There were no conchoidal or asteroid bodies in giant cells, and the lesions lacked the characteristic tight, solid appearance of sarcoid granulomata. Several special staining techniques were used in an attempt to demonstrate the presence of bacteria, including acid fast bacilli or fungi, but all gave negative results. There was no evidence of ova or parasites on careful search.

Postsurgical Course

After surgery, the patient was started on prednisone, 15 mg 3 times a day. This dosage was gradually reduced to 10 mg twice a day by the time of discharge on December 23, 1975, and was maintained until July 1976. After a period in which the dose was tapered, prednisone was stopped in September 1976. The gastrointestinal symptoms have disappeared; the patient has gained weight and her sense of well being has returned. The erythrocyte sedimentation rate, which ranged from 82 to 112 mm per hour prior to steroid therapy, fell to 6 mm. (Westergren). In February 1976 an upper gastrointestinal X-ray series showed no abnormality of the stomach, and minimal changes in the mucosal pattern of the duodenal bulb and post-bulbar area. Endoscopy in March 1976 revealed 3 small punctate erosions of the antrum but was otherwise normal.

Discussion

This 25-year-old woman presented with fever, abdominal pain, anorexia, weight loss. Upper gastrointestinal X-rays revealed thickened, irregular gastric and duodenal folds. The diagnosis of lymphoma or hypertrophic gastritis was considered. At surgery a granulomatous vasculitis limited to the stomach, duodenum, liver and mesentery was found.

The lack of involvement of other layers of the gastric wall besides the submucosa, or of other segments of the gastrointestinal tract, and the participation of vessels differentiate this entity from the pathology found in Crohn's disease. The main component of the lesions in our patient was the vasculitis affecting primarily small muscular arteries. Giant cells were present but there was no necrosis of the arterial wall or apparent involvement of medium or large vessels as in periarteritis nodosa. Also, the distribution of the lesions is peculiar in that they only involved structures in the upper part of the peritoneal cavity and were only related to the upper gastrointestinal tract.

This case stands in contrast to most cases of granulomatous vasculitis in its limited involvement, predominantly of the stomach, duodenum, liver and mesentery. There was no clinical evidence of lung, heart, kidney, skin or central nervous system involvement.

The spectrum of pathologic lesions from angiitis on one hand to granulomatosis on the other has been emphasized (5, 7). From the view point of granulomatous disease of the stomach (8), granulomatous gastritis has been described in disseminated sarcoidosis even when there is no clinical evidence of involvement of the stomach. Regional enteritis may involve the stomach. Isolated granulomatous gastritis has also been described. However, in these three entities, the granulomas do not primarily involve blood vessels.

From the view point of vasculitis with or without granuloma formation, most cases are encompassed by the categories of periarteritis nodosa involving muscular-type arteries, hypersensitivity angiitis involving the smallest branches of intrinsic blood vessels, Wegener's granulomatosis, rheumatic arteritis, allergic granulomatous angiitis as described by Churg and Strauss, and temporal arteritis (6, 7). The role of hypersensitivity in the etiology of these lesions, and the beneficial effect of steroids in some patients has been noted (5).

In 1953, Brill, Churg, and Beaver described allergic granulomatosis associated with visceral larva migrans. They stated that "allergic granulomas are believed to represent a form of response of hypersensitive tissue. The sensitizing factor is assumed to be either bacterial products resulting from repeated respiratory infections, inhaled antigens (such as pollens, drugs or parasites, especially round worms) (9)." Unlike our patient, their patient had marked peripheral eosinophilia, and eosinophilic infiltration of the lesions.

The presence of granulomatosis and vasulitis in our patient raises the possibility of either Wegener's granulomatosis or allergic granulomatosis. Because of the lack of lung or upper respiratory tract involvement, the diagnosis of Wegener's granulomatosis is excluded by definition (4). The patients with allergic granulomatosis described by Churg and Strauss had asthma, lung involvement and eosinophilia (1). The patient described by Abell et al with allergic granulomatosis and massive gastric involvement also had asthma, eosinophilia and pulmonary infiltrates (2).

Recognizing the possible role of hypersensitivity in vasculitis, we instituted a trial of steroid therapy. Remission occurred promptly and was maintained with a moderate dose of prednisone. The subsequent course of the patient remains to be determined, and the question of recrudescence of symptoms and lesions remains open even though remission was maintained after steroids were stopped. Clinicians should be aware that granulomatous vasculitis limited to the upper gastrointestinal tract may occur and may respond to steroid therapy.

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Spontaneous Cervical Hemorrhage due to Ruptured Dissecting Aneurysm of Thyroid Artery: A Case Report and Review of Literature

CHING-SHEN LIN, M.D.

Abstract

A fatal case of spontaneous cervical hemorrhage due to rupture of a dissecting aneurysm of the right inferior thyroid artery is reported. Sixteen cases of spontaneous cervical hemorrhage were collected from the literature. The common clinical symptoms and signs are severe focal pain immediately followed by swelling of neck, difficulty in breathing and/or swallowing and subcutaneous hemorrhage. Suggestive precipitating factors such as sneezing, coughing, vomiting or anticoagulant therapy were present in a number of cases. Although the usual outcome was spontaneous resolution, in infrequent instances, airway compression has become so life threatening that emergency surgical intervention was required.

Introduction

A large spontaneous hemorrhage in the cervical region is an unusual occurrence. It is associated with a characteristic clinical presentation. There is sharp tearing pain, swelling of the neck, difficulty in breathing and/or swallowing, and diffuse ecchymoses in the neck, upper chest and shoulder. Although spontaneous resolution is usual, in a number of instances airway compression has been fatal. Two deaths have been reported and the author describes another fatal case due to a ruptured dissecting aneurysm of the inferior thyroid artery.

Case Report

An 80-year-old white female was admitted on July 1, 1975, because of progressive shortness of breath and pain on the right side of the neck. she was mentally retarded since birth and had a previous admission 2 years ago for congestive heart failure. She was apparently well until the morning of the present admission, when she was found in bed complaining of shortness of breath and pain on the right side of the neck. Examination revealed a hematoma on the right middle portion of the neck. There was no history of trauma. The hematoma progressively enlarged and a hemorrhagic suffusion extended to the right shoulder and beyond the middle line of the neck. The strength of carotid pulsation was equal on both sides. She became dyspneic and the electrocardiogram showed atrial fibrillation with rapid ventricular response. Her blood pressure was 90/50 mmHg and pulse rates were 100 per minute and irregular. Two hours later, she became hypotensive. Supportive therapy was unsuccessful and she died of cardiorespiratory arrest 30 hours after admission.

At autopsy, there was a blue-purple discoloration of the skin of the right side of the neck and shoulder (Fig. 1). On section, there was a hematoma measuring 5.0 cm. in diameter in the right lobe of thyroid and extensive soft tissue hemorrhage in the right side of the neck, right shoulder,

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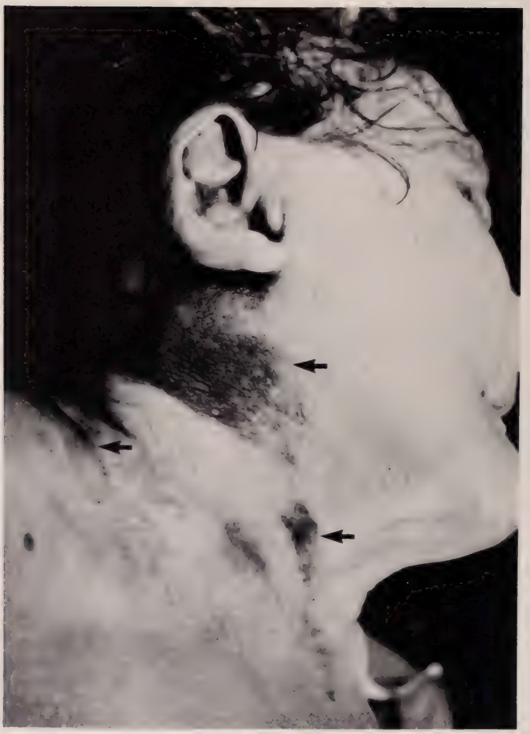

FIG 1. Extensive ecchymotic hemorrhages (arrow) in the right lateral neck and shoulder.

and upper mediastinum. The hemorrhage also insinuated into the soft tissue around the esophagus and trachea. The left lobe of the thyroid was small and fibrotic. The aorta, all of its branches and the major cervical arteries including carotid and thyroid arteries were unremarkable. One small branch of the right inferior thyroid artery, just before its entry into the thyroid, showed narrowing of the lumen with hemorrhage in the wall. Histologic examination of this artery showed multiple focal calcific degeneration of the internal elastic lamina and an intimal laceration with a dissecting hemorrhage (Fig. 2). The right lobe of thyroid showed extensive hemorrhage and the left lobe chronic thyroiditis.

Discussion

Sixteen cases of nontraumatic subcutaneous cervical hemorrhage were collected from the literature. The clinical and pathological features are summa-

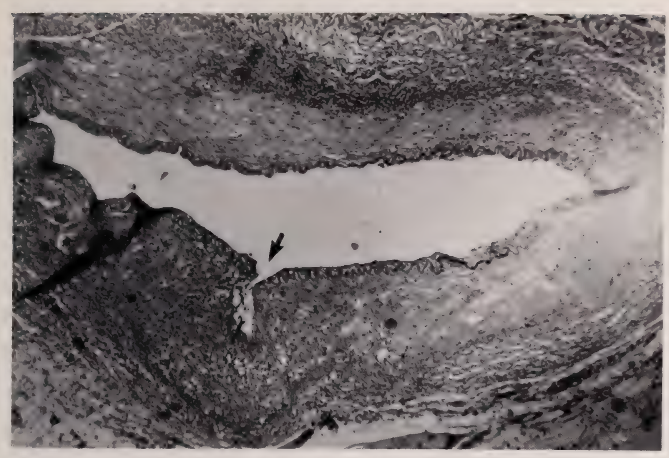

FIG. 2. Photomicrograph of the right inferior thyroid artery showing intimal laceration (arrow) with dissecting hemorrhage in the arterial wall and focal calcific degeneration of the internal elastic lamina. Note: No muscle fibers seen in the hemorrhagic area. (Hematoxylin and Eosin stain 80 ×).

rized in Table I. Most of the cases presented with sharp tearing pain in the neck, immediately followed by swelling and difficulty in breathing and/or swallowing. Ecchymoses of the skin appeared on the neck, upper chest and shoulder several hours to a few days after the onset of pain. In severe cases, hemorrhage could be seen in the pharyngeal mucosa and in the suprasternal notch. Radiographic examination frequently showed widened mediastinum and deviation of the trachea. Angiography was performed in 4 cases (7, 9, 10, 11) but only in one instance (11) was a bleeding source demonstrated. A source of bleeding was found at surgery in 2 cases (6, 11). In each there was a ruptured dissecting aneurysm of the inferior thyroid artery. In 2 other cases, the site of bleeding was determined at autopsy, in one instance from a ruptured parathyroid adenoma (2) and the other from a false aneurysm of a retropharyngeal artery (15). The remaining 12 cases survived, 8 improved spontaneously while the other 4 had an incisional drainage. The source of bleeding was not determined in these 12 cases. Bleeding could have originated from a tear of a small blood vessel; and one of the suggested sites of bleeding is aberrant arteries penetrating the fascia at the thoracic inlet (3, 15). These blood vessels are subjected to the stretching during movements of the neck and head and may possibly rupture after violent coughing, sneezing or vomiting.

TABLE 1

Reported Cases of Spontaneous Cervical Hemorrhage

Case no.	Authors and year published	Age	Sex	Precipitating factors	Treatment	Source of bleeding	Course
1	Capps, 1934	50	M	None	Observation	Parathyroid adenoma	Died
2	Masuelli, 1953	64	F	Hemorrhagic diathesis	Observation	Undetermined	Survived
3	Benedetti-Valentini, 1958	33	M	Muscular exercise	Subtotal thyroidectomy	Undetermined	Survived
4	Epstein, 1960	60	F	Sneezing, coughing	Observation	Undetermined	Survived
5	Epstein, 1960	76	M	Vomiting	Observation	Undetermined	Survived
6	Sandor, 1964	53	M	None	Observation	Undetermined	Survived
7	Sandor, 1964	73	M	Sneezing	None (immediate death)	Retropharyngeal artery	Died
8	Golby, 1965	65	M	None	Tracheostomy; excision of aneurysm	Left inferior thyroid artery	Survived
9	Giroux, 1967	64	F	Anticoagulant	Blood transfusion	Undetermined	Survived
10	Marion, 1968	47	F	None	Tracheostomy; sternostomy for drainage	Undetermined	Survived
11	Reussi, 1969	62		Anticoagulant	Discontinue anticoagulant	Undetermined	Survived
12	Hennessy, 1970	54		None	Observation	Undetermined	Survived
13	Huber, 1971	64	F	None	Observation	Undetermined	Survived
14	Martin, 1974	43	F	None	Excision of aneurysm	Left inferior thyroid artery	Survived
15	Macdonald, 1975	58	F	Sneezing	Thoracotomy for drainage	Undetermined	Survived
16	Owens; Genovesi, 1975	61	F	Anticoagulant	Tracheostomy; neck incision for drainage	Undetermined	Survived
17	Lin, 1977	80	F	None	Observation	Right inferior thyroid artery	Died

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Abnormal Liver Scan in Periarteritis Nodosa

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Introduction

The results of radioisotopic scan of a liver involved by periarteritis nodosa have been reported in only 5 instances. In two (4, 6), the scan was noncontributory, in one (1), there was a large area of decreased uptake which was attributed to a subcapsular hematoma, and in the other two (2, 3), there was irregular or inhomogenous uptake possibly due to arteritis.

Case Report

A 72-year-old male, a native of Turkey, was recently admitted because of epigastric pain and anorexia and fever for the past few days. He had lost 20 lb. of weight over the past two months. Eight years ago, because of pulmonary tuberculosis, he was treated with streptomycin and isoniazid. The physical examination revealed a chronically ill male. His blood pressure was 145/90 mm Hg and temperature 102°F. There was tenderness in the upper quadrant of the abdomen and epigastrium. The liver and spleen were not palpable. Gastrointestinal series and intravenous pyelogram were noncontributory. The pertinent laboratory data were hemoglobin 14.3 gm. %, hematocrit 43%, white blood cells 19,200 cu. mm., erythrocyte sedimentation rate 42 mm. in one hour (Westergren), blood urea nitrogen 21 mg. %, bilirubin 0.8 mg. %, alkaline phosphatase 115 mu/ml., lactic dehydrogenase 205 mu/ml., serum glutamic oxaloacetic transaminase 65 mu/ml., and a trace of albumin as well as a few white blood cells in the urine. The chest x-ray showed bilateral apical fibrosis. Liver scan showed multiple cold areas (Fig. 1), suggestive of metastatic lesions or abscesses. The liver biopsy showed chronic persistent hepatitis. He died suddenly with cardiac arrest 4 weeks after admission.

The autopsy showed periarteritis nodosa involving all visceral organs except for the lung and spleen. There were many hepatic infarcts in areas subtended by hepatic arteries involved by periarteritis nodosa (Fig. 2). A mild chronic persistent hepatitis was also seen. Immunofluorescent study showed that the arterial lesions within the liver and kidney contained Hepatitis-Associated Antigen mixed with IgM and complement.

Discussion

Multiple cold areas in the liver scan were due to the multiple infarcts, while the irregular or inhomogenous uptake could be an expression of arterial involvement.

Since 15% of autopsies in periarteritis nodosa show hepatic infarcts (5), the liver scan can be of diagnostic aid in this disease.

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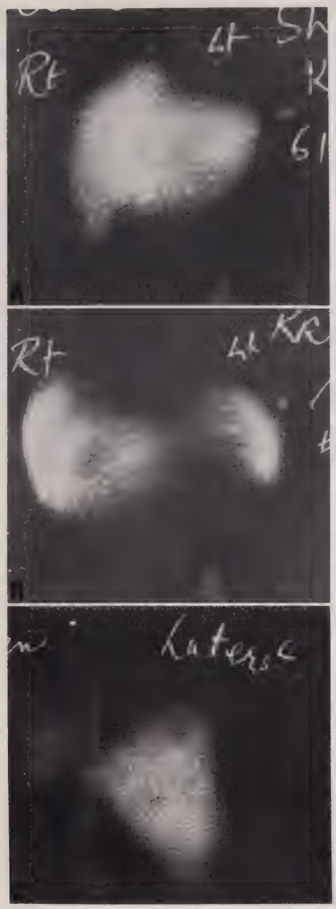
Rt
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FIG. 1. TC^{99m} liver scan showing discrete cold areas in the right and left lobes, A & B anterior view, C lateral view.

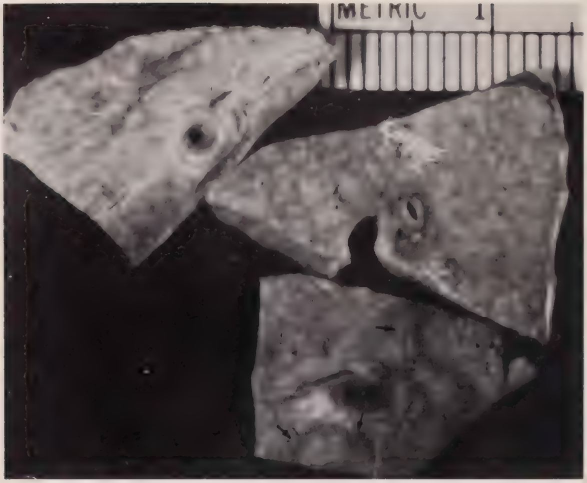

FIG 2. Liver parenchyma showing thrombotic occlusion of hepatic arteries and infarct (arrow).

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The Parotid and the Pancreas
I. The Effects of Secretin, CCK-PZ, and Prostaglandin E_2 on Canine Parotid Secretion

MICHELLE NACCHIERO AND DAVID A. DREILING

This is the first report of a series of experimental and clinical studies attempting to correlate the secretory capacity and pathophysiology of the salivary glands (parotid) and the pancreas.

Salivary secretion is generally considered to be under autonomic control and usually studied following nervous stimulation or following the administration of a parasympathomimetic drug such as pilocarpine, physostigmine, urecholine, etc. This communication investigates the effects of known hormonal regulators of pancreatic flow, i.e. stimulants such as secretin and CCK-PZ and an inhibitor, 16, 16 dimethyl prostaglandin E_2 on salivary secretion.

Method

Parotid secretion was collected in 6 mongrel dogs using a modified Lashley cup. Under phenobarbital anesthesia (0.35 mg/kg I.V.), secretion was stimulated by urecholine infusion (0.24 mg/kg/hr) or by single injection of urecholine (0.25 mg/hr) subcutaneously. Parotid secretion was collected at 5 minute interval for 120 minutes. Each sample was individually analyzed for volume, bicarbonate concentration (Van Slyke), and enzyme (amylase units by Somogyi modification).

The following studies were performed:

A. Urecholine infusion as baseline—after the attainment of a plateau or constant secretion
    1. Constant infusion of secretion (0.06 u/kg/min) or CCK-PZ (0.06 u/kg/min) or both
    2. Constant infusion of pentagastrin (5 μ/kg/hr)
    3. Control—constant infusion of normal saline (50 ml/hr)

B. Urecholine infusion as baseline—after reaching plateau of constant secretion
    1. Single bolus of secretin (1 u/kg) or CCK-P (1 u/kg) subcutaneously
    2. Control—constant infusions of normal saline (50 ml/hr).

C. Urecholine bolus subcutaneously as parotid stimulant with
    1. I.V. bolus secretin (1 u/kg)
    2. I.V. bolus CCK-PZ (1 u/kg)

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D. Urecholine infusion or I.V. bolus as baseline
  1. Single I.V. bolus of increasing dosage of PGE_2 in the unstimulated gland
  2. Single I.V. bolus of increasing dosage of PGE_2 with the parotid secreting in response to urecholine infusion
  3. Single I.V. bolus of increasing dosage of PGE_2 with the parotid secreting in response to urecholine subcutaneous bolus
  4. Indomethacin controls—PGE_2 studies done on dogs following 2 days of indomethacine (5 mg/kg) plus 2.5 mg/kg on the day of experiment

Results

In the urecholine infusion studies (Table I), the hormonal infusions of secretin and CCK-PZ induced within 20–25 minutes a statistically significant increase in bicarbonate concentration ($p < 0.05$) and bicarbonate output ($p < 0.025$). Flow was slightly increased, enzyme concentration and output were unchanged. The hormonal infusion of secretin alone did not affect the urecholine induced secretion; infusions of CCK-PZ, alone, and pentagastrin increased bicarbonate concentration and output.

The data in Table II presents the results of single bolus I.V. secretin and CCK-PZ superimposed on urecholine-induced parotid secretion. Both secretin and CCK-PZ boluses statistically increased flow, bicarbonate concentration and bicarbonate output. Amylase concentration and amylase output were

TABLE I

Urecholine Infusion (0.24 mg/kg/hr)

	No.	Volume (ml/5′)	Bicarbonate		Amylase	
			May. Conc. (mEq/L)	Output (mEq/5′)	Conc. (u/ml)	Output (u/5′)
I. Secretin (0.03 u/kg/min) + CCK-P2 (0.05 u/kg/min) Infusion						
Control	5	5.2 ± .30	49.5 ± 3.2	.22 ± .03	.02 ± .00	.12 ± .01
Secretin + CCK-P2		5.5 ± .18	55.3 ± 3.1*	.32 ± .02**	.02 ± .00	.10 ± .00
II. Secretin (0.06 u/kg/min) Infusion						
Control	4	8.0 ± .10	40.3 ± 1.1	.32 ± .01	.03 ± .00	.24 ± .00
Secretin		8.1 ± .14	40.3 ± 2.3	.30 ± .01	.03 ± .00	.23 ± .00
III. CCK-P2 (.06 u/kg/min) Infusion						
Control	4	7.7 ± .27	30.9 ± 1.0	.23 ± .01	.03 ± .00	.26 ± .00
CCK-P2		8.2 ± .30	41.9 ± 1.7**	.33 ± .01**	.03 ± .00	.26 ± .00
IV. Pentagastrin (5 μ/kg/hr) Infusion						
Control	4	4.7 ± .35	29.4 ± 1.2	.13 ± .01	.02 ± .00	.09 ± .01
Pentagastrin		5.2 ± .15	38.5 ± 2.4**	.19 ± .01**	.02 ± .00	.10 ± .01
V. Normal Saline (50 ml/hr) Infusion						
Control	4	7.7 ± .31	39.1 ± 2.9	.30 ± .02	.02 ± .00	.20 ± .02
Saline		7.3 ± .41	40.4 ± 1.0	.34 ± .02	.03 ± .00	.23 ± .02

* $P < .05$

** $P < .025$

unchanged. Bolus injections of secretin or CCK-PZ (Table III) following urecholine subcutaneously produced variable alterations of secretion which were not statistically significant.

The basal, unstimulated parotid secretion of the unanasthetized canine was unchanged by I.V. PGE_2 (2.5 μ/kg). When this dose of PGE_2 is given superimposed upon a stimulus of constant infused urecholine (Table IV), the parotid flow and bicarbonate output were statistically significantly decreased, p being <0.05 and <0.25 respectfully. On the other hand, bicarbonate and amylase concentrations were significantly increased. Amylase output was not changed. These alterations of secretion induced by PGE_2 were not affected by pretreatment of the dogs with indomethacin. The effect of I.V. PGE_2 at different dosage upon parotid secretion induced by a bolus S.C. urecholine stimulant (Table V) are completely in accordance to those following continuous urecholine infusion, i.e. decreased flow, increased bicarbonate concentration, decreased bicarbonate output, and increased amylase output. In these studies, amylase output is consistently but not significantly depressed.

Table VI presents the changes in Na and K concentrations following urecholine-PGE_2 studies. Na is consistently decreased, K is consistently increased, but the changes are not statistically significant.

TABLE II

Urecholine Infusion (0.24 mg/kg/hr)

	No.	Volume (ml/5′)	Bicarbonate		Amylase	
			May. Conc. (mEq/L)	Output (mEq/5′)	Conc. (u/ml)	Output (u/5′)
		I. Secretin (i u/kg) I.V. Bolus				
Control	4	3.8 ± .18	32.2 ± 1.4	.11 ± .01	.04 ± .00	.15 ± .00
Secretin		4.9 ± .22**	36.2 ± 0.7*	.15 ± .01*	.04 ± .00	.16 ± .01
		II. CCK-P2 (i u/kg) I.V. Bolus				
Control	5	3.1 ± .33	33.0 ± 1.5	.11 ± .01	.04 ± .00	.17 ± .02
Secretin		4.0 ± .22*	38.7 ± 0.7*	.14 ± .01*	.04 ± .00	.17 ± .01

* $P < .05$

** $P < .025$

TABLE III

Urecholine Subcutaneous Bolus (.25 mg/kg)

	No.	Volume (ml/5′)	Bicarbonate		Amylase	
			May. Conc. (mEq/L)	Output (mEq/5′)	Conc. (u/ml)	Output (u/5′)
		I. Secretin (i u/kg) I.V. Bolus				
Control	4	4.5 ± .60	42.1 ± 2.7	.19 ± .03	.04 ± .00	.19 ± .02
Secretin		4.2 ± .50	48.2 ± 2.2	.21 ± .03	.04 ± .00	.20 ± .04
		II. CCK-P2 (i u/kg) I.V. Bolus				
Control	4	3.8 ± .58	46.5 ± 2.2	.22 ± .03	.03 ± .00	.20 ± .04
CCK-P2		3.8 ± .52	53.6 ± 1.9*	.25 ± .03	.03 ± .00	.15 ± .01

* $P < .05$

TABLE IV

Urecholine Infusion (0.24 mg/kg/hr)

	No.	Volume (ml/5′)	Bicarbonate		Amylase	
			May. Conc. (mEq/L)	Output (mEq/5′)	Conc. (u/ml)	Output (u/5′)
I. PGE_2 (2.5 μ/kg) I.V. Bolus						
Control	4	5.0 ± .38	51.6 ± 3.7	.32 ± .03	.02 ± .00	.15 ± .02
PGE_2		2.6 ± .03**	61.0 ± 2.8*	.15 ± .01**	.05 ± .00**	.12 ± .01
II. Indomethacin – PGE (2.5 μ/kg) I.V. Bolus						
Control	2	5.6 ± .03	35.3 ± .7	.19 ± .00	.02 ± .00	.16 ± .00
PGE_2		3.7 ± .10**	45.1 ± 1.7*	.15 ± .00	.04 ± .00**	.16 ± .04

* $P < .05$

** $P < .025$

TABLE V

Urecholine Subcutaneous Bolus

	No.	Volume (ml/5′)	Bicarbonate		Amylase	
			May. Conc. (mEq/L)	Output (mEq/5′)	Conc. (u/ml)	Output (u/5′)
I. PGE_2 (0.3 μ/kg) I.V. Bolus						
Control	3	6.3 ± .72	41.0 ± 2.8	.35 ± .04	.16 ± .01	1.03 ± .17
PGE_2		4.9 ± .43*	47.8 ± 2.8*	.31 ± .02	.22 ± .01**	.85 ± .12
II. PGE_2 (0.5 μ/kg) I.V. Bolus						
Control	4	5.6 ± .88	45.2 ± 7.1	.44 ± .03	.17 ± .01	.65 ± .06
PGE_2		4.9 ± .58*	63.9 ± 2.3*	.39 ± .05	.20 ± .02*	.57 ± .08
III. PGE_2 (1.0 μ/kg) I.V. Bolus						
Control		4.2 ± .69	53.5 ± 2.5	.31 ± .03	.07 ± .00	.45 ± .08
PGE_2		2.8 ± 1.08*	63.0 ± 4.8*	.27 ± .11	.11 ± .00**	.35 ± .10
IV. PGE_2 (2.5 μ/kg) I.V. Bolus						
Control		3.9 ± .43	39.8 ± 2.3	.21 ± .04	.14 ± .02	.61 ± .01
PGE_2		2.6 ± .37*	43.2 ± 2.3*	.17 ± .02	.18 ± .06*	.47 ± .01

* $P < 0.5$

** $P < 0.025$

TABLE VI

Urecholine Infusion, 0.24 mg/kg/hr

	Na Conc. (mEq/L)	K Conc. (mEq/L)
Urecholine Control	108.7 ± 6.1	6.7 ± .44
Urecholine + PGE_2 0.3 I.V. Bolus	107.7 ± 5.4	7.4 ± .29
Urecholine Control	100.3 ± 3.3	5.6 ± .70
Urecholine + PGE_2 0.5 I.V. Bolus	94.3 ± 4.3	5.9 ± .40
Urecholine Control	124.0 ± 2.9	10.2 ± .02
Urecholine + PGE_2 1.0 I.V. Bolus	117.5 ± 1.8	13.4 ± .06
Urecholine Control	105.6 ± 3.3	6.5 ± 1.54
Urecholine + PGE_2 2.5 I.V. Bolus	104.3 ± 8.6	5.4 ± .69

Discussion

The fundamental purpose of these studies was to determine whether the parotid gland was susceptible to the hormonal stimuli which evoke pancreatic secretion, with the intent of setting up a test of parotid secretion which might supplement the findings of secretin-CCK-P2 pancreatic responses in patients with and without pancreatic disease.

The data clearly indicate that the parotid response to pancreatic stimulants (secretin and CCK-P2) as well as inhibitors of secretion (PGE_2) is concordant with their effects on the pancreas. It, therefore, is possible to study parotid secretion during the secretin or secretin-CCK-P2 tests so that correlation of both secretory responses in an individual patient is possible.

Summary and Conclusion

The effect of pancreatic secretagogues and inhibitors on parotid secretion in the dog has been described. In general secretin and CCK-P2 produce concordant responses in the parotid and pancreas. A test correlating pancreatic and parotid secretion after secretin or secretin-CCK-P2 is suggested.

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The Parotid and the Pancreas
II. Parotid Secretion in Canine Chronic Pancreatitis

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In the recent literature, there have been reports of parallel functional and histologic changes in the pancreas and parotid of rodents with experimental pancreatitis (1). In a preliminary clinical investigation of parotid secretion in patients with and without pancreatic disease, the same authors reported in the former group a diminution of parotid flow, a decline in bicarbonate concentration, and a decrease in amylase output, secretory alterations which are similar to the changes in pancreatic secretion observed in end stage chronic pancreatitis (2). This study was undertaken to investigate the sequential changes in parotid and pancreatic secretion during the development of experimentally produced canine chronic pancreatitis (3).

Method

Ten mongrel dogs weighing 20–25 kg were prepared with Thomas pancreatic fistulas following ligation of the lesser pancreatic duct. Six dogs were used as controls. The remaining 4 animals were subjected to 2400 Rads T.D. to the pancreas delivered on alternate days in 6 exposures of 400 Rads T.D. each. This regimen has been shown to produce histologic chronic pancreatitis with marked secretory pancreatic insufficiency (3). At the end of the studies, this pathology was confirmed by biopsy in each animal.

Testing Pancreatic Function. All dogs were trained to stand quietly in a Harvard frame. They were studied in the conscious state deprived of food but not water for 18 hours. A standard secretin test (1 unit/kg) and Secretin-CCK-PZ test (Secretin 0.03 u/Kg/min plus CCK-PZ 0.05 u/kg/min) were performed at least 3 times in all dogs initially and were repeated weekly for the duration of the study. Pancreatic secretion was described in terms of 15' flow (ml.) bicarbonate output (mEq.) and enzyme output (mg. protein/15') as well as maximum bicarbonate concentration of MEq./L.) and enzyme concentration (mg. protein/ml.).

Testing Parotid Secretion. The dogs, similarly fasted, were anesthetized with phenobarbital injected intravenously in a dose of 0.35 mg/Kg. The animals were placed on their left side and the right parotid papilla was covered with a standard saliva sampling cup. After stimulation, saliva was collected

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under oil in 5' periods for 30'. Each dog was studied 3 times. Parotid secretion was measured in terms of flow (ml/5'), bicarbonate concentration (MEq/L) and output (M Eq/5') and enzyme concentration (U.Amylase/ml.) and output (u amylase/5').

Preliminary studies using the classical stimulus, pilocarpine infusion or subcutaneous bolus (Table IA) had to be supplemented by standardizations with an alternate stimulus, urecholine (Table IB) because pilocarpine was not available.

The data in Table IC indicates that urecholine (0.24 mg/kg/hr) infusion and urecholine (0.25 mg/kg) bolus are satisfactory stimuli producing secretory responses corresponding to the classical administrations of pilocarpine. The latter seems to have a greater effect on bicarbonate and a lesser effect on amylase than the former.

Open biopsies were done in the control and irradiated dogs. Pancreatography was performed on all animals. Analytic data is presented as mean ± S.D. A student T-Test was used to determine statistical significance.

Results

The sequential changes in pancreatic secretion following irradiation of the pancreas are presented in Table II. The data indicates that except for a transient increase in flow and bicarbonate output, neither statistically significant, there is a progressive decrease in all parameters during the study. The data is statistically significant at 8 weeks, at which time marked pancreatic insufficiency is evident.

The sequential changes in parotid secretion after pancreatic irradiation are presented in Table III. It is quite evident that these secretory alterations do not parallel those observed in the pancreas. In fact, the trends are opposite, i.e.

TABLE I

Parotid Responses to Pilocarpine and Urecholine

	Flow (ml/5')	Bicarbonate Conc. (mEq/L)	Bicarbonate Output (mEq/5')	Amylase Conc.	Amylase Output
A. Classical Parotid Stimulus					
1. Pirocarpine infusion (0.24 mg/kg/hr)	3.2 ± .18	63.4 ± 1.33	.19 ± .01	.02 ± .00	.07 ± .00
2. Pirocarpine S.C. Bolus (0.25 mg/kg)	3.9 ± .66	68.0 ± 3.37	.29 ± .04	.02 ± .00	.07 ± .00
B. Urecholine Titrations					
1. Subcutaneous Bolus					
0.125 mg/kg	1.3 ± .42	42.4 ± 2.6	.07 ± .01	.04 ± .01	.14 ± .04
0.25 mg/kg	4.3 ± .74	43.6 ± 3.0	.20 ± .03	.06 ± .01	.27 ± .06
0.5 mg/kg	4.7 ± .73	51.7 ± 4.7	.30 ± .05	.06 ± .01	.28 ± .03
1.0 mg/kg	5.9 ± .72	60.5 ± 2.6	.39 ± .04	.07 ± .01	.43 ± .07
2. Continuous Infusion					
0.24 mg/kg/hr	3.8 ± .18	34.5 ± 1.5	.13 ± .08	.04 ± .01	.11 ± .01
0.48 mg/kg/hr	5.6 ± .31	45.3 ± 2.5	.25 ± .02	.04 ± .01	.22 ± .02
0.96 mg/kg/hr	5.7 ± .47	56.5 ± 2.2	.30 ± .04	.05 ± .01	.28 ± .02
C. Accepted Standard Urecholine Stimulus					
1. S.C. 0.25 mg/kg	3.8 ± .18	34.5 ± 1.5	.13 ± .08	.04 ± .01	.11 ± .01
2. I.V. 0.24 mg/kg/hr	4.3 ± .74	43.6 ± 3.0	.20 ± .03	.06 ± .01	.27 ± .06

TABLE II

Sequential Pancreatic Responses to 0.3 u/kg/min Secretin Before and After Irradiation of the Pancreas

Control	Volume (ml/15′)	Bicarbonate C (mEq/L)	Bicarbonate 0 (mEq/15′)	Protein C (mg/ml)	Protein 0 (mg/15′)
6 observations	26.8 ± 2.4	128.9 ± 2.9	3.45 ± 0.01	4.12 ± 1.87	110.5 ± 0.80
2 Weeks After X-ray 3 observations	32.6 ± 3.9	127.4 ± 9.0	4.15 ± 0.02	2.85 ± 0.85	93.0 ± 0.15
4 Weeks After X-ray 4 observations	27.8 ± 2.3	118.1 ± 7.3	3.28 ± 0.02	3.04 ± 0.27	84.6 ± 0.25
6 Weeks After X-ray 2 observations	21.0 ± 2.7	119.0 ± 3.4	2.49 ± 0.04	2.75 ± 0.45	57.6 ± 0.80
8 Weeks After X-ray 4 observations	9.4 ± 3.3*	97.5 ± 12.2	0.91 ± 0.01*	2.75 ± 0.46*	25.9 ± 1.12*
3 Months After X-ray 4 observations	9.0 ± 4.9*	87.8 ± 19.1*	0.79 ± 0.03*	2.83 ± 0.86*	25.6 ± 1.25*
4 Months After X-ray 3 observations	2.0 ± 0.8**	92.4 ± 6.5*	0.18 ± 0.04**		

* S.p < 0.010
** S.p < 0.0010

TABLE III

Sequential Parotid Responses to Urecholine 0.25 mg/kg s.c. Before and After Irradiation of the Pancreas

Control	Volume (ml/min)	Bicarbonate C (mEq/L)	Bicarbonate 0 (mEq/min)	Amylase C (U/ml)	Amylase 0 (U/ml)
4 observations	0.8 ± 0.04	40.6 ± 3.30	0.03 ± 0.01	0.85 ± 0.1	0.73 ± 0.2
6 Weeks After X-ray 3 observations	1.0 ± 0.15	43.7 ± 3.70	0.04 ± 0.01	0.85 ± 0.26	0.84 ± 0.1
8 Weeks After X-ray 3 observations	1.1 ± 0.20	48.9 ± 4.79	0.05 ± 0.015	0.81 ± 0.16	0.88 ± 0.2
3 Months After X-ray 3 observations	1.4 ± 0.15*	47.4 ± 2.51	0.06 ± 0.016	0.37 ± 0.9*	0.32 ± 0.1
4 Months After X-ray 3 observations	1.2 ± 0.09*	42.9 ± 2.50	0.05 ± 0.015	0.44 ± 0.08	0.51 ± 0.1**
8 Months After X-ray 5 observations	0.24 ± 0.06***	32.3 ± 2.27***	0.01 ± 0.0***	0.06 ± 0.01***	0.014 ± 0.004***

* Sp < 0.010
** Sp < 0.025
*** Sp < 0.0010

as pancreatic secretion diminishes, there is augmentation of parotid response. Only 8 months after pancreatic irradiation, is there a statistically significant decline of parotid secretion. A comparison of the 4 month and 8 month data clarifying these relationships are summarized in Table IV.

Histologic section of the pancreas disclosed advanced chronic pancreatitis, atrophy and fibrosis in the irradiated dogs. Biopsy of the parotid did not show any differences in histology between the control animals and the pancreatic irradiated dogs.

Discussion

The present study indicates that the induction of chronic pancreatitis and pancreatic insufficiency in dogs by pancreatic irradiation is accompanied initially by a hypersecretion of the parotid gland involving flow, bicarbonate

TABLE IV

Comparison of 4 and 8 Month Post Pancreatic Irradiation Parotid Secretory Data

Control	4 Months after irradiation	8 Months after irradiation
Volume		
0.8 ± 0.04 ml/min	1.2 ± 0.09 ml/min ↑ S: $p < 0.005$	0.24 ± 0.06 ml/min ↓ S: $p < 0.001$
Bicarbonate Concentration		
40.6 ± 3.3 mEq/L	42.9 ± 2.5 mEq/L ↑ N.S.	32.3 ± 2.27 mEq/L↓ S: $p \simeq 0.050$
Bicarbonate Output		
0.03 ± 0.001 mEq/min	0.05 ± 0.015 mEq/min ↑ N.S.	0.01 ± 0.006 mEq/min ↓ S: $p < 0.001$
Amylase Concentration		
0.85 ± 0.1 mg/ml	0.44 ± 0.08 mg/ml ↓ S: $p < 0.001$	0.06 ± 0.01 mg/ml ↓ S: $p < 0.001$
Amylase Output		
0.73 ± 0.2 mg/ml	0.65 ± 0.1 mg/ml N.S. $p = 0.5$	0.014 ± 0.004 mg/min ↓ S: $p < 0.001$

output but not amylase secretion. After 8 months this hypersecretion was followed by hypofunction.

The mechanism involved is not clear. Increased sensitivity of the parotid gland to urecholine or ductular reduplication without change in acinar mass in response to trophic feedback mechanisms released by the diseased pancreas could explain the parotid hypersecretion. Light microscopy, however, did not show any histologic changes.

The data are not concordant with Kakizaki's studies in which a parallelism was observed in the parotid and pancreatic secretion in experimental pancreatitis as well as in patients with clinically manifest pancreatitis. Type of insult, duration of disorder, and in the clinical series the possibility of direct toxic effect of the inciting agent, presumably alcohol, may explain the discordance.

Conclusion

Pancreatic and parotid function studies were compared between normal dogs and those with chronic pancreatitis induced by radiotherapy. Parotid hypersecretion in the latter group was observed initially with augmentation of bicarbonate output and no change in amylase output. Later, parotid secretion is depressed. This suggests a compensatory phenomenon followed by either exhaustion or glandular toxicity. It does cast doubt, however, on the use of parotid secretion as an accurate estimater of pancreatic disorder.

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Outpatient Physician Scheduling: The Use of Work-Rate Probability Estimates*

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MICHAEL M. STEWART, M.D., M.P.H.

Introduction

Directors and administrators of hospital-based ambulatory care programs are repeatedly confronted with the need to achieve the most efficient utilization of available physician service time, whether obtained on a salaried or voluntary basis. Proper scheduling of outpatient department (OPD) physicians can be a complex and difficult task in ambulatory care settings characterized by factors such as varying broken-appointment rates in different types of clinics, contrasting physician work-rates in appointment clinics as compared to clinics receiving unscheduled (walk-in) patient visits, and wide variations in the work patterns of individual attending physicians and house officers.

Several approaches have been reported to the problem of maximizing use of professional resources in health care settings. Prescriptive approaches have attempted to specify staffing norms based on observed workload requirements and identification of the numbers and types of personnel judged necessary to dispose of this workload (1–3). Other investigators have attempted to project the total annual number of visits to an ambulatory care program or to specific types of clinics (e.g., Pediatrics, Obstetrics, General Medicine) by obtaining data on sociodemographic characteristics for a sample of clinic users and then applying utilization norms to estimate the total number of expected visits (4–6). Additional methods include: categorization of patient visits either as "initial" or "follow-up" and the use of arbitrary time standards for each type of visit in order to allocate physician resources (7); attempts to change patient behavior by instituting a centralized appointment system (8); and overbooking of patients to compensate for broken appointments (9).

Some of these approaches require knowledge and skills which are usually beyond the technical capability of OPD administrators, and some are costly and time-consuming. More important, many of these published reports fail to reflect an adequate understanding of the complexity of OPD operations. For example, one assumption made in some of the more sophisticated statistical approaches is that clinic workload is stable and predictable, whereas this often is not the case. Also, it is often assumed, for purposes of planning and resource allocation, that most patients will keep their appointments, while in reality the

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related problems of broken appointments and unscheduled visits continually haunt the OPD administrator (10).

The situation at City Hospital Center at Elmhurst, one of several large municipal hospitals in the system operated by the New York City Health and Hospitals Corporation, illustrates some of the important issues and problems in making maximum and effective use of OPD physician time. During 1975, there were 396,000 total OPD visits to the 85 clinics at City Hospital Center at Elmhurst. Clinics vary widely in terms of total patient volume, number of scheduled sessions per week, use of appointment systems, and inter-clinic referral policies. Staffing patterns reflect widely differing mixes of full-time attending physicians, sessional physicians and house officers at various levels of training (11, 12). The recent fiscal crisis in New York City has led to a series of mandated and unprecendented budget reductions at Elmhurst. As a consequence, routine managerial concern for proper resource allocation has given way to a continuing intensive investigation of possible options for the best use of shrinking OPD resources in ways that will minimize any negative impact on quality of care. For the past 18 months, the hospital's Budget and Program Review Committee has reviewed in detail the current budgets and operations of all departments and has explored all reasonable options for reduction of costs.

This report describes a method, initially developed at the request of the Budget and Program Review Committee, for monitoring physician work-rate in the OPD so that slack resources can be allocated or, in some cases, eliminated through inclusion in the hospital's overall budget reduction plan. However, this method is sufficiently generalizable to be applicable in other OPD's of similar complexity where there is serious administrative concern for efficient use of available physician resources.

Description of the Method

The OPD physician-assignment method presented here is based on the following assumptions: 1) that the number of patient visits per time period to any specific clinic is best predicted by using recent historical data to calculate the mean and standard deviation for actual patient volume per clinic session; 2) that although the amount of time a physician spends with each patient can vary widely, there is relatively little variation from the mean figure for overall physician work-rate (number of minutes per patient or number of patients per hour) for all of the individual patient-physician contacts which occur during the operation of a given clinic session; 3) that patient arrival rate is constant during a given clinic session; and 4) that OPD physicians are the persons most capable of identifying the two extremes of physician work-rate which represent the acceptable upper and lower limits beyond which clinic physicians are either overworked (too few patients per physician per clinic session) or underutilized (too few patients).

Use of the physician-assignment method makes it possible to compute the probability that the average physician work-rate for a particular clinic will remain within acceptable limits for appropriate utilization of available OPD physician time, given the total number of patient visits scheduled for an OPD clinic session and the total number of physician-hours available. Physician "overloading" implies insufficient time to perform the necessary clinical tasks and a probable reduction in the quality of ambulatory care, whereas "underloading" implies waste of expensive OPD physician resources.

The probability of total clinic attendance (number of patients) can be readily estimated for any specific clinic session. For example, assume that a particular clinic has recently had a mean attendance figure of 100 patients per clinic session (fixed number of hours per session), with a standard deviation of 20. In order to determine the probability that more than 120 patients will attend a future clinic session, a "*Z* value" can be computed using the following formula:

$$Z = \frac{(\text{expected no. pt. visits} - \text{mean no. pt. visits})}{\text{standard deviation}}$$

$$Z = \frac{(120 - 100)}{20} = \frac{20}{20} = 1$$

This "*Z* value" can then be used to estimate the probability of total attendance of more than 120 patients at a future clinic session. Figure 1 shows the relationship between this "*Z* value" and the probability of total clinic attendance for the example described. As shown in the figure, when $Z = 1$, there is an 84% probability of 120 or less patients attending a clinic session. Therefore, there is only a 16% probability (100%–84%) that more than 120 patients will need to be seen during a future clinic session by the available pool of physicians in the hypothetical clinic described. The curve shown in Figure 1 is based on an application of the statistical concept of a normal frequncy distribution.

Given the total number of patients expected to attend a clinic session, an empirically-determined mean for physician work-rate (patients per physician per scheduled clinic hour) can be used to calculate the total number of physicians needed to provide these clinic services in the future, if mean physician work-rate remains constant:

$$\text{no. of physicians needed} = \frac{\text{total no. pts. seen}}{\text{scheduled physician hrs.} \times \text{work-rate}}$$

Most important for this discussion is the estimated probability that physicians assigned to a particular clinic will be able to adhere to a work-rate which lies within accepted limits of OPD physician utilization and productivity, in terms of number of patients seen per actual physician-hour invested. The probability that physicians in a given clinic will have to work at a mean rate less than a specified work-rate norm can be calculated as follows:

$$P = \frac{f(W \times D \times T - M)}{\text{Sd}}$$

where

P is the probability of a work-rate lower than the norm
f is the normal cumulative frequency distribution
W is the work-rate norm
D is the number of doctors present
T is hours of clinic session operation
M is mean patient attendance per clinic session
Sd is standard deviation of patient attendance per clinic session

A *physician underload probability* (P_u) is computed using the above formula with P equal to P_u and W as the underload work-rate norm. Using the same formula, a *physician overload probability* (P_o) can be computed where $P_o = 1 - P$, if W is assigned the overload work-rate norm. The probability of achieving an acceptable work-rate (P_A), that is, a work-rate between specified overload and underload work-rate norms, is expressed as $P_A = 1 - (P_o + P_u)$.

Application of the Method

The physician-assignment method was first developed using a hand calculator and elementary statistical tables. To simplify calculations for the large number of clinics involved, a computer program was written in Fortran IV to compute the probabilities of underload and overload for specific clinics. Program inputs were: available clinic statistics on patient volume, numbers of physician-hours assigned, and acceptable physician work-rate norms. These norms were determined through discussion with physicians in the individual

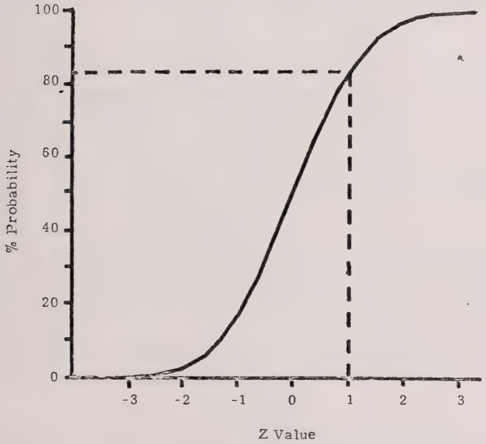


FIG. 1. Workload probability calculation.

clinics studied. Outputs of the computer program included session summary statistics, per cent of sessions with underload and overload, and expected work-rate probabilities. Data from one appointment clinic and one walk-in clinic at Elmhurst are shown in Tables I and II.

The Hematology Clinic (Table I) operates two three-hour clinic sessions per week, with an average of four doctors in attendance and approximately 10 patients per session. The clinic attending physicians were interviewed and it was felt that a range of 1.5–3.0 patients per physician-hour in this clinic represented an acceptable physician work-rate.

One pressing administrative question was whether the Hematology Clinic might be able to fulfill its clinical responsibilities by operating for one rather than two clinic sessions per week without reducing the quality of care provided. If all patient visits were scheduled during a single three-hour session, recent data on clinic attendance indicate that mean patient attendance would be 20–21 patients per session. Estimates of the mean work-rate probabilities for individual physicians assigned to a combined clinic are shown in Figure 2.

From the figure it can be seen that the current policy of assigning four physicians for the entire clinic session leads to a 32% probability of underload and a zero probability of overload. By contrast, the use of only three physicians would lead to a 10% probability of underload and a 12% probability of overload, reducing the overall probability of not achieving an acceptable work-rate from 32% to 22% (10% + 12%). Also, as shown in Table I, a decision to combine the two clinic sessions into a single session with four physicians would increase the mean work-rate from about .9 to 1.7 patients per physician-hour, which is well within the acceptable work-rate limits identified by the clinic physicians as appropriate for this clinic.

TABLE I

Hematology Clinic

Session	Mean patient attendance	Standard deviation	Mean physician attendance	Mean work-rate (pts./MD hour)
Tuesday	9.85	3.41	4	.82
Friday	10.83	2.33	4	.90
Combined	20.50	5.50	4	1.70

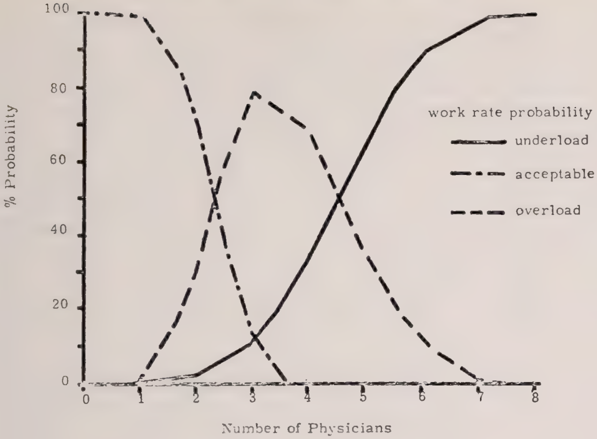
TABLE II

Diagnostic Clinic

	No. of Physicians	.5	1	1.5	2	2.5	3	3.5
Probability	Underload	0	0	0	1	36	95	100
	Overload	100	100	45	0	0	0	0
	Acceptable	0	0	55	99	64	5	0
	Mean Work-Rate	20.8	10.4	6.9	5.2	4.2	3.5	3.0

Underload work-rate <4 patients/physician hour

Overload work-rate >7 patients/physician hour



underload = 1.5 pts. /md hr.
overload = 3 pts. /md hr.

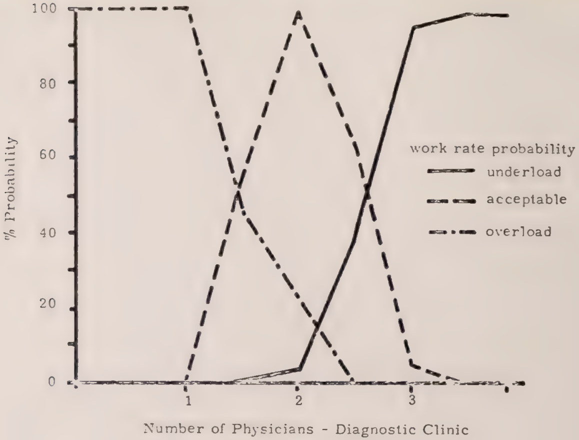
FIG. 2. Work-rate probabilities—hematology clinic.

The physician-assignment method was also applied to the Diagnostic Clinic, an adult walk-in clinic. Here a budget reduction had been imposed and it was necessary to determine how to reduce physician sessional monies with minimal effects on patient care. The Friday clinic session was studied since mean attendance for this day of the week was 83 as compared to 112 for Monday, suggesting that a substantial reduction might be possible in physician-hours assigned. Current staffing consists of three physicians for this eight-hour session. Acceptable work-rates were determined to be four to seven patients per physician-hour. Given the current staffing pattern, the probability of underload on Fridays is 95% (Table II, Fig. 3), and the mean work-rate is only 3.5 patients/physician-hour (Table II).

A decision was therefore made to reduce the staff from 3 to 2 physicians for the Friday session. The physician-assignment method estimated that following this change, the expected workload would remain within the desired range 99% of the time, with a minimal chance of either underloading or overloading. As shown in Table II, it is anticipated that this will increase the efficiency of physician utilization without exceeding acceptable work-rate norms.

Discussion

The use of work-rate probability estimates for OPD physician scheduling is a relatively simple technique with powerful predictive capability. The sched-



underload < 4 patients/md hr.
overload > 7 patients/md hour

FIG. 3. Work-rate probabilities—diagnostic clinic.

uling of physicians can be adjusted to accomodate to predicted patient volumes without imposing work-rates which would be judged inappropriate by physicians. It is important to underscore the fact that this method respects and incorporates physicians' own estimates of the work-rate appropriate to the type of service being provided, and of the upper and lower work-rate limits should not be exceeded.

The method is flexible enough to be applied to all types of clinics, independently of size or type of appointment system. It can be adjusted for variations in patient volume by day of week or time of day. The more data available, the more finely can staffing patterns be adjusted. For example, adjustments for recurrent seasonal variations are currently being developed at Elmhurst.

Snce greater efficiency is obtained by adjusting staffing patterns, the identification of underloading offers an administrator several options. These include: reducing the number of sessions per week; reducing the length of the session; or adjusting physician staffing patterns. Another alternative is to divert workload from areas of overutilization of those of underutilization to the extent that it does not violate physician work-rate norms. For example, nonacute cases could be diverted from an emergency room to a walk-in clinic or to a general medical clinic. Identification of slack physician resources also allows the reallocation of physician hours from outpatient to inpatient services.

It should be noted, however, that while this method maximizes the efficient use of physician time, it does not address the important issue of patient waiting time. It is intuitively obvious, for example, that in an underloaded clinic which uses a block appointment system and where there may be a large group of patients already waiting at the start of a clinic session, increasing physician work-rate by increasing the patient volume will also lengthen patient waiting time. Concurrent attention must therefore be given to systems of appointment scheduling (13).

The two examples discussed above highlight the usefulness of the physician-assignment method. Aside from the potential for maximizing physician productivity while respecting work-rate norms, a reduction of one Hematology Clinic session per week would free up space and ancillary personnel for other purposes. The variability in workload between Diagnostic Clinic sessions allowed the identification of a specific session for which physician staffing has been reduced by one with a minimal probability that the upper work rate norm will be exceeded.

An administrator can also use this method in setting priorities. For example, where physician resources are scarce, it might be decided that some clinics can (or must) accommodate a higher probability of overloading than other clinics. On the other hand, certain clinics could be intentionally underloaded. For example, if problem-oriented records were being instituted or if there were a significant investment of clinic physician time in the education of medical students or house staff, underloading might be necessary and appropriate. The physician assignment method can also be used as an evaluation and monitoring tool when there is an expressed concern about possible overloading of clinics, and as a planning tool when developing a new or reorganized clinic program.

Finally, although this project was completed with computer assistance, small-scale efforts can be readily accomplished with a hand calculator using statistical methods familiar to most health care administration program graduates.

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Pathophysiology of Jaundice and Modern Diagnostic Approach to Jaundice Patient

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Clinical jaundice derives from physiologic derangements which can be classified as:

1) prehepatic
2) intrahepatic
    a) hepatocellular
    b) postlobular
3) posthepatic
    a) hepatocholecdochal
    b) pancreatic

This simplistic grouping (Table I) has a surgical bias rather than a pathophysiologic biochemical orientation since the primary goal of the surgeon treating patients with jaundice is to separate obstructive from nonobstructive cases. With the diversity of methods available at the present time, a failure to do so is an unacceptable error. Diagnostic laparotomy for jaundice can only be condoned in patients acutely ill with sepsis whose general condition does not permit use of the full diagnostic armamentarium.

There is no need to rehash the valuable clues in the clinical course of illness but it should be stressed that pertinent data, e.g.,

1) hepatotoxic medication
2) existing blood dyscrasia
3) familial occurrence of jaundice
4) biliary colic
5) recent anesthesia
6) stool color
7) RVQ abdominal signs
8) RVQ mass
9) evidences of sepsis and/or hypotension

should influence the physician in the sequence with which he employs the following laboratory diagnostic techniques;

1) Biochemical Analysis
    a) blood
    b) urine
    c) stool
2) X-ray
    a) routine G.I.

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TABLE I

Prehepatic	Hepatocellular	Posthepatic
Serum	*Liver* Cell	Duct System
		Canaliculi→Duct—CD—Papilla
Bilirubin-Protein	$\boxed{\overrightarrow{\text{Conjugation}}}$	Bilirubin-Glycuronate
Overload	Enzymatic Failure Excretory Block	Cholestasis-Obstruction
Blood Disorder	Liver Disease-Metabolic Disorder	Stone-Stricture-CA

   b) hepatocholangiography
   c) C.A.T.
3) Function Studies
   a) liver
   b) pancreatic
4) Isotopic Scanning
5) Sonography
6) Endoscopy
7) Liver Biopsy
8) Laparoscopy
9) Cytology
10) Arteriography

Biochemical analysis is the initial step in diagnostic sequences. It is noninvasive, least expensive, and immediately available. The simplest and most useful determinations would be:

1) hepatic enzymes—SGOT, SGPT, 5α-N
2) alkaline phosphatases
3) conjugated and unconjugated bilirubin

The diagnostic flow chart illustrated in Table II affords a neat preliminary separation of jaundiced patients for the surgeon. It must be emphasized that this division is preliminary and not infallible. There is considerable overlap of biochemical data among patients with hepatitis, cholestatic jaundice, and extrahepatic obstructive jaundice. The schema is valuable in suggesting further diagnostic sequence. For example, if the diagnosis is between hepatitis and cholestatic jaundice a liver biopsy should disclose the pathology. If the choice is between cholestatic jaundice and obstructive jaundice, a secretin test and/or retrograde endoscopic cholangiography would be diagnostic. The flow chart would be as indicated in Table III.

Although biochemical analysis of stool, duodenal contents, and urine for bilirubin and its derivatives are routinely performed, these examinations are really more useful in assessing the completeness of obstruction rather than the type.

Once the familial hyperbilirubinemias, hepatitis, and cholestatic jaundice have been excluded the task is that of determining the nature and site of obstruction. *X-ray* would be the next technique. A routine flat film of the abdomen followed by upper GI series may disclose:

1) gallstones
2) G.B. displacements and calcinosis
3) lesions in the pancreatic head

Hypotonic duodenography can significantly improve the recognition of pathology in the periampullary region.

Obstruction to biliary flow can be pinpointed by one of two techniques:

1) those disclosing mass
2) those outling biliary passages

TABLE II

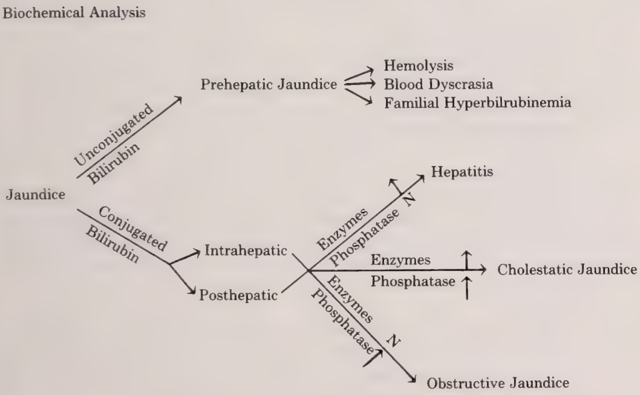
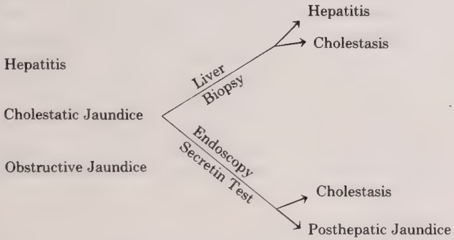

Biochemical Analysis
Jaundice
Unconjugated Bilirubin
Prehepatic Jaundice
Hemolysis
Blood Dyscrasia
Familial Hyperbilrubinemia
Conjugated Bilirubin
Intrahepatic
Posthepatic
Enzymes ↑ Phosphatase N
Hepatitis
Enzymes ↑ Phosphatase ↑
Cholestatic Jaundice
Enzymes N Phosphatase ↑
Obstructive Jaundice

TABLE III


Hepatitis
Cholestatic Jaundice
Obstructive Jaundice
Liver Biopsy
Hepatitis
Cholestasis
Endoscopy Secretin Test
Cholestasis
Posthepatic Jaundice

At present both techniques are experiencing a mushrooming of methods and refinement.

Demonstration of mass by barium displacement is now considered a late manifestation of tumefaction. Rather, mass may be indicated by

1) ultrasound (esp. fluid)
2) CAT scanning
3) isotopic scintillography (Te^{99}, Ga)
4) arteriography

Scanning with technetium^{99} is most useful for metastatic tumors, Gallium scanning is capable of demonstrating abscess. Arteriography, in our hands, has been less rewarding, affording mainly serendipitous data.

Outlining the biliary tract most exquisitely localizes the site of biliary obstruction. Cholangiography may be accomplished by the following techniques:

1) Physiologic Cholangiography
    a) Oral Cholecystography
    b) Intravenous Cholangiography
2) Instrumental Cholangiography
    a) Peroral Endoscopic
    b) Percutaneous Transhepatic
    c) Transjugular (Hepatic Venous)
    d) Laparoscopic

A gallbladder and intravenous cholangiography are generally of minimal use in the differential diagnosis of jaundice. Both depend upon liver function to transport the dye from the blood to the bile ducts. In jaundice, regardless of pathogenesis, this function is impaired. Indeed the tests are contraindicated since retained iodinated dye may be toxic to the liver itself as well as to the G.B. and kidney.

Instrumental cholangiography on the other hand is being used with greater frequency and success. When feasible the positive and negative evidence of endoscopic cholangiography generally confirm the diagnosis and help in the surgical treatment. The alternate instrumental techniques are not without danger but do provide the essential data when endoscopy is unsuccessful. Parenthetically, laparoscopy is an underutilized technique in the States. Under direct vision it is possible with safety to locate masses, to biopsy them, to aspirate the gallbladder, and to inject the biliary tract.

Study of hepatic and pancreatic function have a limited value in diagnosis. BSP retention would not be diagnostic, nor would its derived test with radioactive Rose Bengal scanning be of help in distinguishing the various types of obstructive jaundice. The value of the secretin test, though limited to patients with endoscopy failure, is illustrated in Table IV. Cytologic examination of the duodenal drainage after secretin is useful in confirming malignancy.

Immunologic titres such as:

1) Australian Antigen
2) Antimitochondrial Antibodies
3) Antinuclear Antibodies

TABLE IV

Secretin Test	Biliary Flow	Lesion
1) Abnormal	Abnormal	CA Head Pancreas
2) Normal	Abnormal	Extrahepatic Obstruction CD Stone Structure, or CA
3) Normal	Normal	Hepatocellular Jaundice (Cholestasis)

4) α-Fetoprotein

and examination of the stool for ova and parasites were omitted from the diagnostic technique since these data are more apt to disclose etiology rather than pathophysiology.

Finally, the surgeon is often faced with a most difficult problem, namely postoperative jaundice. This is a most perplexing complication of operations which taxes the surgeons diagnostic skill. It should never be sidestepped by such meaningless phrases as nonspecific postoperative hepatitis. Postoperative jaundice derives from a combination of diverse factors:

1) Increased Bilirubin Load
    a) Hemolytic Anemia
    b) Transfusion Hemolysis
    c) Resorption of Hematoma
2) Impaired Hepatocellular Function Induced by
    a) Anesthesia Halothane
    b) Drugs—Antibiotics, Antimetabolites
    c) Shock
    d) Viral Infection
3) Cholestasis Caused by
    a) Hypoxia, Hypotension
    b) Drugs
    c) Sepsis
4) Duct Obstruction due to
    a) Operative Injury
    b) Retained stones
    c) Abscess

Differential diagnosis, thus, can be as complex as in patients entering the hospital with jaundice.

The laboratory and new instrumentation have made diagnosis of the jaundiced patient an exercise in logic. One must conclude by repeating an initial statement: Diagnostic laparotomy for jaundice cannot be condoned.

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Factors Influencing Survival of Colorectal Cancer

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Abstract

110 cases of long-term survivors and 91 cases of short-term survivors, following surgical treatment of colorectal carcinoma, were reviewed. No significant difference was found in age, sex, incidence of bleeding, abdominal pain, and concurrent adenomatous polyps between the two groups. Weight loss, obstruction, and palpable abdominal mass were more frequently seen among the short-term survivors as presenting symptoms.

The most significant finding in this study was the fact that left colonic carcinoma did better than cecal lesion not only in stage B and C lesions respectively, but also C lesions of the left colon did better than B lesions of the cecum.

Although preoperative values of carcinoembryonic antigen and peripheral lymphocyte counts have been reported recently to be useful prognostic indicators in colorectal carcinoma, the Dukes' pathological staging remains the most reliable prognostic factor (1–3).

A retrospective study was made of 201 cases of colorectal carcinoma who underwent surgical treatment at the Mount Sinai Hospital, New York, New York, to determine what other factors might be related with the outcome of surgical treatment. A comparison was made between the long term survivors and non-survivors in regard to the age, duration and types of symptoms, anatomical sites and pathological stages of the tumor.

Materials and Methods

110 cases of long-term survivors and 91 cases of short-term survivors were selected for the study. Of the 110 long-term survivors, 104 patients survived more than 5 years, six survived 4 years. Of the 91 patients who died within 5 years of surgery, 74 (81%) died within 2 years. The age, sex, clinical history, operative findings, and pathological reports were reviewed.

The presence or absence of symptoms listed in Table II were recorded. If more than one symptom existed in a patient, all were taken into consideration.

The follow-up was obtained through the Tumor Registry and/or by direct contact with referring physicians.

The duration of symptoms was defined as the period from the onset of a symptom or symptoms attributable to colorectal carcinoma to the time of diagnosis. The pathological stage was determined by review of the operative findings and pathology reports. Dukes' classification was used for staging: A)

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tumor confined to the mucosa, B) tumor involving the entire wall of the bowel without nodal involvement, C) lymph node involvement, and D) distant metastasis. The incidence of concurrent polyps found within the resected surgical specimen was also compared between the two groups.

Results

Age distribution and sex: No significant difference was found in age distribution between the long term survivors and non-survivors. There were 113 males and 88 females. Neither were there significant differences in survival in relation to sex (Table I).

Duration of symptoms: The mean duration of symptoms of the survivors was 6.2 months, and that of those who died 5.3 months.

Presenting symptoms and concurrent polyps: No significant difference was found in presenting symptoms between the survivors and non-survivors. There was a significant difference in the incidence of weight loss between the two groups (18%:25%). Obstruction and palpable mass were much more common clinical features among the non-survivors (Table II). When the presenting symptoms are analysed according to the anatomical sites of the lesions a high

TABLE I

Age and Sex

Age	No. cases		Male		Female	
	Surv.	Death	Surv.	Death	Surv.	Death
30–39	1	2			1	2
40–49	6	3	4	1	2	2
50–59	13	15	7	7	6	8
60–69	51	37	29	26	22	11
70–79	31	27	19	16	12	11
80	8	7	3	1	5	6
Total	110	91	62	51	48	40

TABLE II

Presenting Symptoms

Symptoms	Survivors (110 cases)		Deaths (91 cases)	
	No.	Percent	No.	Percent
Abdominal pain	29	26.3	29	31.8
Anemia (occult bleeding)	11	10.0	2	2.1
Overt bleeding per rectum	55	50.0	47	51.6
Weight loss	20	18.1	23	25.2
Change in bowel habit	28	25.4	21	23.0
Obstruction	4	3.6	7	7.0
Palpable abdominal mass	1	0.9	7	7.6
Tenesmus	1	0.9	1	1.0
Others	1	0.9	1	1.0
Asymptomatic	1	0.9	0	—
Concurrent polyps	19	17.0	21	23.0

percentage of overt bleeding is noted with lesions closer to the rectum while the opposite is noted in relation to occult bleeding (Table III).

Anatomical site of tumors: Anatomical distribution of the tumors is shown in Table IV. A striking difference was found in survival rate between the right side and sigmoid colonic tumors. Of 48 cases of cecal lesions, 19 survived and 29 died (40%:60%), whereas of 64 cases of sigmoid lesions 45 survived and 19 died (70%:30%). It was particularly interesting to note that not only did the sigmoid colonic lesions in stage B and C respectively have a better survival rate as compared to the cecal lesions, but also stage C lesions in the sigmoid colon had a better survival rate than the stage B lesions of the cecum (Table V).

Pathological stage: The survivor group had more stage A and B lesions as compared to the non-survivor group which had more stage C and D lesions (Table VI).

Surgical procedures: Accepted cancer surgery was performed on all the cases by wide resection of bowel and mesentery with intent of cure except for stage D lesions where palliative resection was performed.

Discussion

Our study shows that the presenting symptoms of colorectal carcinoma have no prognostic value, and shows that some symptoms are related with the

TABLE III

Symptoms According to Anatomic Site

Symptoms	Right colon		Transverse colon		Left colon				Rectum	
					Descending		Sigmoid			
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Pain	15	29.0	16	59.0	2	40.0	21	32.0	4	7.0
Anemia (occult bleeding)	8	17.0	3	11.0	0	—	1	2.0	1	2.0
Overt bleeding	11	23.0	10	37.0	3	60.0	34	53.0	44	77.0
Weight loss	23	47.0	7	26.0	0	—	8	12.0	5	8.0
Change in bowel habit	10	21.0	5	19.0	1	20.0	17	26.0	16	28.0
Obstruction	2	4.0	3	11.0	0	—	3	6.0	2	3.0
Abdominal mass	6	12.0	0	—	0	—	1	2.0	1	2.0
Others	0	—	0	—	0	—	2	4.0	2	3.0
No symptoms	1	—	0	—	0	—	0	—	0	—

TABLE IV

Distribution According to the Anatomical Sites

	Survivor	Death	Total
Cecum	19	29	48
Transverse colon	6	3	9
Splenic flexure	9	9	18
Descending colon	5	0	5
Sigmoid colon	45	19	64
Rectum	26	31	57
Total	110	91	201

TABLE V

Long-Term Survivor in Stage B and C

	Total no.	No. survivor	Percent
Stage B (104 cases)			
Right colon	22	12	54
Sigmoid	36	30	83
Rectal	27	18	66
Stage C (66 cases)			
Right colon	18	6	33.3
Sigmoid	15	10	66
Rectal	23	8	34.7

TABLE VI

Pathological Stage

Stage (Dukes)	No. survivors	No. non-survivors
A	6	0
B	75	29
C	27	40
D	2	22

anatomical location of the tumors; overt bleeding as a presenting symptom is more associated with left sided lesions while the opposite is true of occult bleeding. No appreciable difference was found in regard to age distribution between the survivors and nonsurvivors. Difference in the presenting symptoms is explainable on the basis of anatomical sites of the lesions. Those who died had a shorter duration of symptoms and presented at more advanced pathological stages of disease as compared to the long term survival group. This suggests that tumors in those who died have a faster growth rate and perhaps, are more virulent than the tumors of those who survived.

The most striking finding in this study was the fact that sigmoid carcinoma had a much better survival rate as compared to right sided colonic carcinoma to the extent that even stage C sigmoid carcinoma did better than stage B right colon carcinoma. Falterman (4) et al suggested that the reason that left colonic carcinomas have a better survival rate as compared to the right colonic lesions is because of delayed discovery of the latter lesions. However, this speculation is not sufficient to explain the better survival rate of stage C sigmoid lesions over the stage B right sided lesions. Perhaps, there is a difference in biological behavior.

This study points out that clinical features do not have prognostic value in colorectal carcinoma. The study, however, supports the previous study showing that left sided colonic carcinoma has better prognosis than the right sided lesions (4–6). Improved results of left sided carcinoma do not appear to be related to duration of symptoms or more favorable pathological stage. It appears that improvement of results in treatment of colorectal carcinoma will not come by mass screening or reliance on symptoms for early detection, but rather by better knowledge of biological behavior of host tumor relationships.

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Polymicrobial Septicemia from an Intravenous Catheter

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The importance of meticulous care and frequent changing of intravenous catheter sites has been repeatedly emphasized (1-3). To underscore this point, we report the following case of a patient who developed polymicrobial septicemia following prolonged intravenous catheterization, with five organisms isolated from the catheter tip and three from the bloodstream.

Case Report

A 77-year-old man was admitted to Beth Israel Hospital because of congestive heart failure. He had sustained a left cerebrovascular accident one year previously. Pulmonary congestion improved on a cardiotonic regimen, but early in the hospital course, urethral catheterization was required because of acute urinary retention. Twenty-four hours following insertion of the catheter, the patient developed a fever of 104°F accompaned by hypotension. Cultures of urine and blood subsequently yielded Proteus mirabilis. Therapy, consisting of fluids, corticosteroids, and antibiotics, successfully eliminated the infection, but acute renal failure and increased mental obtundation ensued, as a result of the hypotensive event. Initially fluids and medications were administered through peripheral intravenous lines which were changed every seventy-two hours. Subsequently, however, a polyethylene catheter was aseptically inserted through a cutdown into the right antecubital vein and remained in place for nine days, following which the patient again developed fever and shaking chills. Two blood cultures each were positive for Proteus mirabilis, Citrobacter freundii, and Streptococcus fecaelis. Culture of the intravenous catheter tip showed the following five organisms: Proteus mirabilis, Streptococcus fecaelis, Streptococcus viridans, Enterobacter cloacae, and Enterobacter species. Urine and sputum cultures were negative and no site other than the intravenous catheter was clinically implicated as a source for the septicemia. The patient responded to discontinuation of the catheter and appropriate antibiotics, with prompt defervescence and sterilization of the bloodstream. His subsequent course, however, was complicated by cardiac and renal failure, and on the forty-eighth hospital day he suffered a cardiac arrest from which he could not be resuscitated.

Discussion

Infection is the most serious and common complication of intravenous cannulation (4). Migration of skin flora, contamination by hospital personnel during catheter insertion or manipulation, or hematogenous seeding during unrecognized bacteremic episodes have been implicated as sources of bacterial colonization of indwelling lines (5-7). Maki and coworkers in their extensive review (8) recommend that catheter tips be cultured in every case of unexplained fever, clinical sepsis, phlebitis, catheter malfunction, and when a catheter has been in place for longer than forty-eight hours. This approach

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becomes all the more vital in view of the possible development of polymicrobial septicemia.

The incidence of mixed bacterial sepsis has been reported to range from 6 to 10 per cent of all bacteremic episodes (9–11). Enhanced susceptibility to multiple organism bloodstream invasion has been observed in the acute leukemic patient (12), and has been attributed to the leukopenic state and the presence of oral and intestinal ulcerations commonly seen in this population (13). Hermans and Washington (14), in their analysis of 49 episodes of polymicrobial sepsis in 46 patients, found, in addition to hematologic malignancies, a high incidence of underlying gastrointestinal disease, particularly when obstruction of the common bile duct or of an intestinal viscus had occurred. Underlying abnormalities of the urinary tract, in contrast, were noted in a significantly lower percentage of cases of polymicrobial sepsis than usually encountered in unimicrobial gram negative sepsis. Eleven percent of the total cases in this series were post-operative cardiac surgery patients; it was in this group that iatrogenic factors, consisting of multiple intravenous polyethylene catheterizations for recording of hemodynamic parameters and administration of intravenous solutions, were implicated in the bacteremic event. The overall mortality in this review was 37 percent and correlated with the severity of the underlying disease.

The case we present dramatically illustrates the fact that the number of different organisms which can proliferate on the tip of an indwelling intravenous catheter is unlimited. Although the terminal event in our patient was not directly related to acute septicemia, it was no doubt the result of the late complications of shock, namely cardiac and renal failure. It is frequently the most complicated patient and therefore the one who can tolerate sepsis least well, who will most often require multiple intravenous cannulations for proper management. Certainly many emergency situations requiring intravenous polyethylene catheters are resolved in 48 to 72 hours. It is at this point that the need for their continued use must be carefully scrutinized, and weighed against the very real risk of catheter-associated uni- or polymicrobial septicemia. Stainless-steel needles of the scalp vein type represent a sound alternative for intravenous infusions since infectious complications with these devices are significantly less likely than with polyethylene catheters. (1).

Conclusions: (1) In addition to removal of the intravenous line, the empiric use of combined drug therapy for broad spectrum antimicrobial coverage is justified when intravenous catheter-associated septicemia is suspected. (2) The development of polymicrobial septicemia in a hospitalized patient should call attention to the possibility of an infected intravenous catheter as a likely source. (3) Scalp vein needles should be employed whenever possible for routine intravenous infusions.

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Endometrial Stromal Sarcoma and Leiomyosarcoma Arising in Adenomyosis: A Possible Presentation of Occult Extra-Genital Malignancy

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Abstract

The development of sarcomatous stromal changes in an adenomyoma is described. The changes occurred in an elderly patient, who was found at autopsy to have an anaplastic cecal carcinoma of oat cell type, histologically distinct from the stromal tumor. In view of the known hormonal capability of these anaplastic tumors and the frequency with which postmenopausal uterine activity relates to increased estrogens, it is suggested that the elaboration of a hormonally active substance by the cecal tumor may have resulted in stimulation of the adenomyoma with neoplastic transformation. Precedent for this suggestion is to be found within previous accounts of endometrial stromal malignancy occurring in association with certain presumably hormonally active tumors. It is recommended that an occult carcinoma be sought for in the postmenopausal patient who demonstrates evidence of active endometrial or myomatous growth in the absence of any known source—either exogenous or endogenous—of estrogenic hormones.

Uterine stromal sarcoma arises only infrequently in endometriosis (3, 8, 10) and we have been able to find only one account of its development in adenomyosis (4). We have been unable to find a previously reported example in which both endometrial stromal sarcoma and cellular leiomyoma occurred concurrently within an adenomyoma.

Clinical Data

This seventy-five year old gravida two, para two, Caucasian female had a normal menstrual history and uneventful menopause. She was now admitted with a rapid onset of lower abdominal pressure and pain. She was minimally hypertensive. Pelvic examination revealed a nontender, symmetrical pelvic mass filling the cul-de-sac and extending to the level of the umbilicus. The adnexae were not palpable. An IVP showed some ureteral compression and a barium enema showed compression of rectal wall without evidence of infiltration. Exploratory laporotomy disclosed a large mass involving the uterus. The mass was adherent to the bowel and parietal peritoneum. The cul-de-sac was occupied by a second mass, cystic, hemorrhagic, and necrotic, with some areas of chocolate coloration, apparently derived from the main mass. The adnexae were not involved in the tumor. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed.

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Pathologic Findings

The specimen was received by the laboratory in three parts, of which two were portions of friable, gray-tan, partially hemorrhagic tissue. Some areas had a "brain-like" appearance. The third part consisted of a uterine mass with grossly normal attached adnexae.

On microscopic examination it was apparent that both endometrial stromal sarcoma and a cellular myoma were present and that both had arisen from a preexisting, atrophic adenomyoma. The myomatous areas were cellular, with plump nuclei and mitotic activity (Figs. 1, 2). We actually believe this to represent leiomyosarcoma of low grade. Endometrial glands were not observed in the myomatous areas. Within other sections proliferation of endometrial glands and stroma filled entire fields which were completely devoid of muscular elements. The endometrial glands were hyperplastic, but not carcinomatous (Fig. 3). The glands were embedded in a cellular stroma which had undergone frank sarcomatous transformation in areas. The sarcomatous foci formed diffuse sheets, from which glands were absent. (Figs. 4, 5) Remnants of the benign myoma were present, and within this scattered atrophic endometrial glands were seen (Fig. 6). The ovaries were not atrophic, but were not obviously hyperplastic. The patient was treated with chemotherapy and irradiation. She succumbed three years after her initial admission supposedly of her uterine disease. At autopsy, however, no residua of the uterine sarcoma were found, but a large carcinomatous tumor involved the cecum transmurally and presented microscopic features similar to those of bronchial 'oat cell carcinoma'

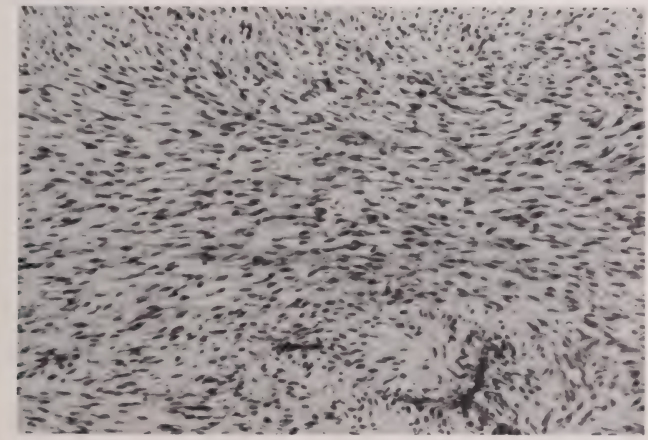

FIG. 1. Highly cellular myoma. Compact cellular bands of smooth muscle fibers are seen (H & E × 80).

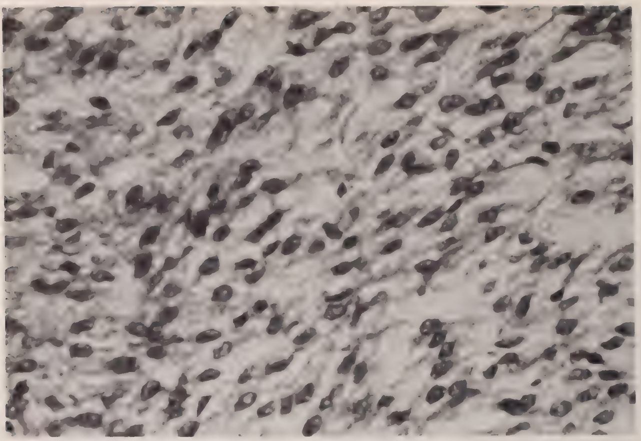

FIG. 2. High power view of preceding area. Nuclei are plump, hyperplastic, pleomorphic. A mitotic figure is shown (H & E × 200).

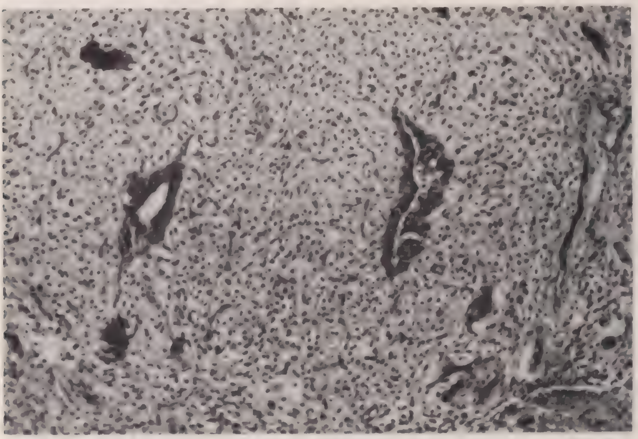

FIG. 3. Endometrial glands within the mass. They are hyperplastic and are surrounded by masses of proliferating stroma (H & E × 80).

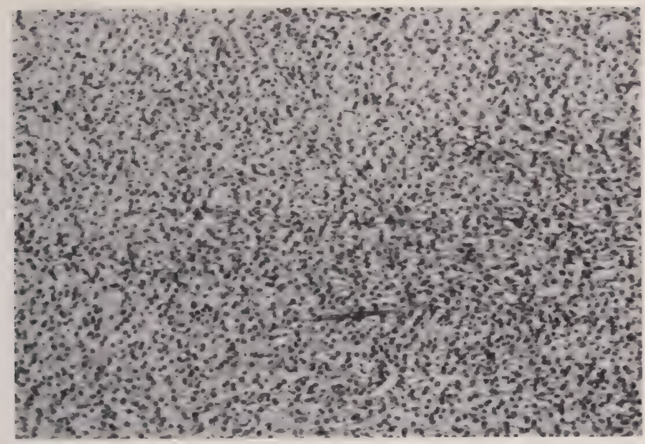

FIG. 4. Frank endometrial stromal sarcoma. A sheet of proliferating endometrial stroma is seen (H & E × 80).

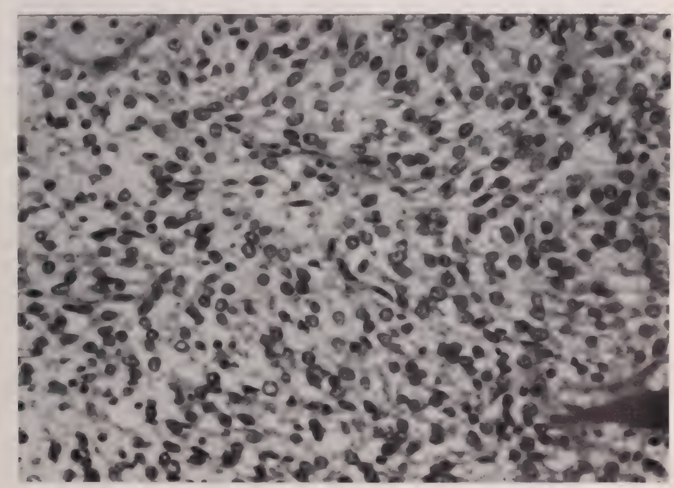

FIG. 5. High power view of the preceding showing spindle shaped stromal cells (H & E × 200).

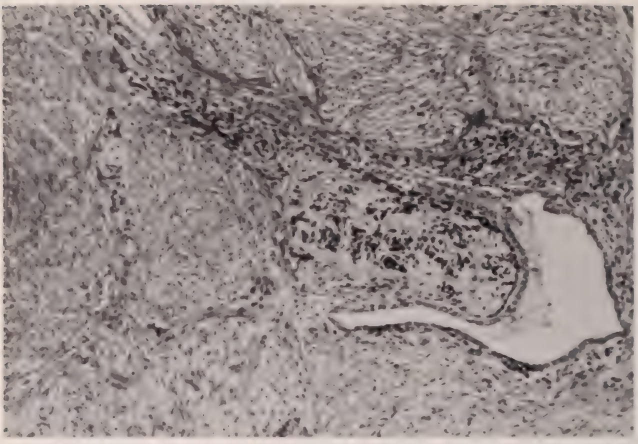

FIG 6. Atrophic areas of adenomyoma, showing smooth muscle fibers and an endometrial gland lined by low cuboidal epithelium. The endometrial stroma related to the gland displays a plexiform pattern (H & E × 80).

(Figs. 7, 8). As no bronchial lesion was detected, it was assumed that the cecal growth was primary. Metastatic deposits were widespread. Multiple sections of vagina and exocervic showed mucosal denudation with focal epithelial islands showing radiation change, precluding any estimate of estrogenic activity.

Discussion

While adenocarcinoma is the malignancy of most frequent development in ectopic endometrium (2, 6), the development of endometrial stromal sarcoma within such endometrium is well documented (3, 4, 8, 10). Again, adenocarcinoma most frequently comes to mind as the product of abnormal estrogen stimulation. Malignant proliferation of endometrial stroma, particularly ectopic, in response to such stimulation, has, to our knowledge, rarely been addressed (1, 11). The finding of a highly cellular smooth muscle tumor, concomitant with the stromal malignancy, in an adenomyomatous complex, also appears to be unique; yet it is not surprising that the muscular component should respond to a hormonal stimulus in unison with the other elements, the muscle proliferating actively with the glandular and stromal components, as may well be seen in extrauterine adenomyomas.

Of particular interest in this case is the presence of a tumor of oat cell type. The occurrence of oat cell tumors within the gastrointestinal tract has previously been recorded (7, 12). Tumors in this category have been associated with ectopic ACTH secretion (5, 9), and it may be suggested that some steroid hormone produced as a result of adrenal cortical stimulation may here have

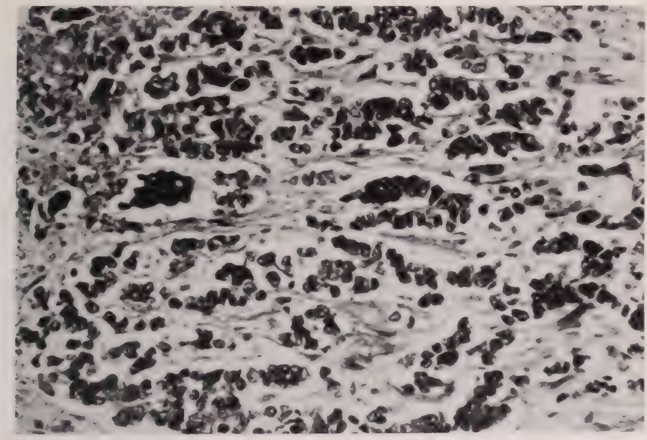

FIG. 7. Anaplastic carcinoidal tumor of the cecum. Cords of cells are shown (H & E × 200).

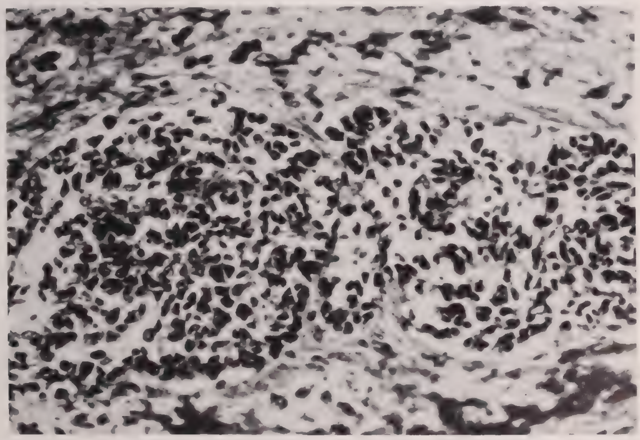

FIG. 8. Anaplastic carcinoidal tumor of the cecum. The tumor cells are spindle shaped and present an 'oat cell' morphology (H & E × 200).

been responsible for the sudden initiation of growth in an adenomyomatous complex which was probably inactive. Precedent for this suggestion is to be found in previously reported instances of endometrial stromal malignancy occurring in association with certain ovarian tumors (1, 11) that were, presumably, hormonally active. In the absence of an ovarian tumor or exogenously administered hormone, it is not unreasonable to speculate that the undetected colonic neoplasm provided the necessary stimulus for the uterine malignancy. It may be recommended that the presence of an occult extragenital tumor be excluded in any postmenopausal patient who manifests evidence of sudden endometrial activity in the absence of a known endogenous or exogenous estrogenic source.

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Long-Term Follow-Up of Polymyalgia Rheumatica

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Polymyalgia rheumatica (PR) is an entity that is now well recognized and a substantial number of patients with this entity are seen. A major problem with PR relates to its association with Giant Cell Arteritis (GCA). There are a number of reports that in many patients with PR a temporal artery biopsy revealed GCA, even in patients in whom no clinical evidence of arteritis is present (1–4). In some series the incidence is as high as 41 percent (4). It has, therefore, been suggested by some authors that in *all* instances PR is a manifestation of an underlying GCA. The implication of this is quite serious. Whereas, classically, the symptoms of PR respond to and are readily controlled by low doses of corticosteroids (5), GCA is a threatening illness which carries with it a substantial risk of complications including blindness, stroke, and dissecting aneurysm (6–8). The dose of corticosteroid traditionally used in the treatment of GCA consequently is far greater than that used in PR (9). Therefore, it carries with it the risk of serious side-effects, particularly in the elderly (10).

If, indeed, PR is a manifestation of an underlying GCA then all patients with PR may be at great risk for the complications of GCA and should be treated accordingly, in spite of the hazards involved. If, on the other hand, the patient with PR is not prone to develop the complications of GCA, then it would certainly be far preferable to treat him with the smallest dose of corticosteroid necessary to control his symptoms. This communication addresses itself to our experience in relation to this particular problem.

Materials and Methods

Patients with a typical PR syndrome have been followed by the authors from four to nine years. The criteria for inclusion in this series are set forth in Table I.

Some comments as to these criteria are in order. Though some patients with a PR syndrome may have pain only in the pectoral or pelvic girdles, for the purposes of this communication such patients were excluded. A number of workers have reported that patients with typical PR may be accompanied by synovitis, particularly in the knees (2, 11, 12). However, in our view, such patients are difficult to distinguish from those with rheumatoid arthritis in the elderly, particularly those exhibiting the bilateral shoulder-hand syndrome. When our knowledge of the etiology and pathogenesis both of PR and rheu-

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TABLE I

Criteria for Polymyalgia Rheumatica

1. Severe pain and stiffness of the pectoral and pelvic girdles, generally with rapid onset.
2. Constitutional symptoms including lassitude, fever, and weight loss.
3. No objective evidence of synovitis.
4. Erythrocyte sedimentation rate elevated over 60mm/hr Westergren.
5. Normal "muscle" enzymes.
6. No clinical evidence of GCA: specifically, absence of severe headaches, visual disturbance, swollen tender temporal artery, joint claudication, or bruits over large vessels.
7. Full and rapid clinical response to 10 mg of prednisone a day or less.

matoid arthritis are better defined, such distinctions may not be necessary, but in order to clearly define a group which we call PR, we regard it as preferable that the distinction between PR and rheumatoid arthritis be as clearcut as possible.

The dosage criterion of response to 10 mg prednisone per day or less was included because there are many conditions that will respond dramatically to high doses of prednisone, whereas in our experience the dramatic and complete reversal of clinical and laboratory findings with 10 mg of prednisone is highly characteristic of PR as opposed to other diseases wherein higher doses are necessary to achieve a similar type of response (in only two of our patients have 15 mg of prednisone per day been necessary).

The clinical features of our patients conform to the criteria in Table I. There were 56 patients: 39 females and 17 males. Three were under 60, and only 5 were over 80. The vast majority were in their seventh and eighth decades.

Fourteen patients underwent temporal artery biopsies. All of these were negative. There was no particular selection as to which of our patients underwent temporal artery biopsy and we do not routinely biopsy the temporal artery in patients with PR. However, the temporal artery is biopsied in patients who have symptoms or signs suggestive of cranial GCA. Indeed, a patient with the PR syndrome who has severe headache, visual disturbance, claudication of the jaw, or other evidences of systemic arteritis, in spite of a negative biopsy, is regarded as having GCA and treated accordingly.

As noted above almost all our patients were treated with 10 mg of prednisone a day or less and all have responded. When the patient was virtually free of symptoms, administration of the steroids was slowly tapered. When the patient was symptom-free, the dose was tapered further. The sedimentation rate was followed and almost invariably fell with treatment. However, the presence of an elevated sedimentation rate in an otherwise asymptomatic patient did not deter us from further decreasing the corticosteroid dose. The patients were followed closely; initially, at two week intervals and then at longer intervals. At each follow-up visit the patient was specifically asked about the presence of headache or visual disturbance and the temporal arteries were palpatated. Fundoscopic examination was routinely performed.

No patient has become blind or manifested any visual disturbance. One patient on a routine follow-up visit was found to have asymptomatic blurring of her optic discs. Bilateral temporal artery biopsy was negative. Complete neurologic examination and investigation were similarly unrevealing. Increase of the prednisone dose from 7-2 mg to 60 mg a day did not alter the fundoscopic findings. The patient died two years later of a coronary artery occlusion. On postmortem examination, no evidence of arteritis could be found. Just recently, one patient (not included in the present study) with PR who had been under excellent control for two years developed a severe unilateral headache. Temporal biopsy was performed and showed GCA. The steroid was increased to 40 mg per day and her headaches disappeared. She is well now on 20 mg of prednisone a day, though she has sustained collapse of two vertebrae. No visual disturbances or complications of arteritis have occurred in this patient. This bears out our contention that careful and continued observation of our patients precludes losing sight of an emerging arteritis.

The results of the follow-up study are shown on Table II. Eight patients have died, 5 of coronary artery occlusion; in none of these was there any indication that coronary arteritis was present. Postmortem examination was available only in one patient (the one referred to above). In four of the five, the PR was in remission at the time of death and the patients were off corticosteroids. Two patients have died of carcinoma; one of the uterus and one of the colon. One of these patients was off steroids and the other was taking 2-½ mg of prednisone daily. One other patient died of a mesenteric thrombosis. Careful examination of the bowel that was resected at surgery showed only atherosclerotic changes and no evidence of arteritis was present.

Of the survivors, 35 are off corticosteroids and are relatively well. Thirteen still require 5 mg of prednisone a day or less to control symptoms. This finding is in contrast to early reports that the PR syndrome runs its course within two years (13, 14). Steroid complications have been minimal; one patient has developed glaucoma and one dyspepsia. Thus the small dose of steroids used in this group of patients has been tolerated very well and certainly has improved their quality of life.

In contrast, Table III shows our experience with biopsy-proved GCA relative to steroid side effects. Of 22 patients, 10 have developed substantial steroid toxicity as indicated by four with vertebral collapse, four with disabling steroid myopathy, two with complicated ulcer disease, one with uncontrolled diabetes, and one patient became overtly psychotic. (There were 17 complications in 10 patients.) The dose of steroid necessary to control *symptoms* in this group was usually far higher than necessary to control similar symptoms in the PR group. Of the 22 patients with biopsy-proved GCA 10 have become blind. This high incidence of blindness reflects the fact that many of these patients were

TABLE II

Mortality in Polymyalgia Rheumatica

Coronary arteriosclerosis	5	(4 patients in P.R. remission)	
Carcinoma	2	(1 patient in P.R. remission)	All of steroids
Mesenteric thrombosis	1	(1 patient in P.R. remission)	
Arteritis	0		
Total deaths	8		

TABLE III

Steroid Complications (Patients with T.A.)

Vertebral collapse	5
Disabling steroid myopathy	3
Complicated ulcer disease	2
Uncontrolled diabetes millitus	3
Psychosis	3
HIP Fracture	1
Total	17

initially referred either by the neurology service or ophthalmology service after blindness had already supervened. This high incidence of blindness, though, is comparable to that which has been reported in the literature (13), but is probably much higher than a true incidence of blindness in GCA. In this group of 22 patients with GCA of whom 10 became blind, 3 of them had polymyalgia rheumatica-like symptoms before blindness occurred. However, all of these patients had had severe headache, scintillating scotomata, visual disturbance or other symptoms suggestive of cranial arteritis before they became blind. Thus, these patients even though manifesting symptoms of PR had other clinical findings that suggested the presence of GCA, and prompt treatment with proper corticosteroid dosage may have prevented the unfortunate result.

Discussion

PR is a common entity and a painful one. Patients suffering from it are in a great deal of distress. Small amounts of prednisone (5) will render these elderly patients symptom free and allow them to maintain their independence and live a useful life. However, the spectre of an underlying cranial arteritis causes great concern to the physician taking care of the patient with this entity. In this regard even a negative temporal artery biopsy certainly does not exclude the presence of a cranial arteritis, as we have seen a number of patients who have a typical picture of cranial arteritis and whose temporal artery biopsies were negative. Therefore, it is essential to know the degree of risk of these patients developing blindness, strokes or the other disastrous complications associated with cranial arteritis. On the basis of the experience described, it is our conclusion that patients with the PR syndrome who have no clincal evidence of GCA and whose symptoms can be controlled with small amounts of steroids are at very little risk for the development of complications of cranial arteritis. Therefore, they may be rendered symptom-free rather quickly, allowed to function normally, and yet not be subjected to the potentially disastrous side effects of a high dose of corticosteroids. This is a purely practical point and in no way addresses itself to the presence or absence of an underlying arteritis in these patients. Further studies as to the natural history of both GCA and PR are necessary before this question can be defined. Most particularly, postmortem studies are necessary to see if, indeed, an underlying arteritis is present. In the meantime, the physician faced with the problem of caring for the patient with PR can safely treat with the small dose of steroid necessary to render the patient symptom-free. Under proper observation and supervision there exists an extremely low and acceptable risk of developing the complications of cranial arteritis.

Summary

Fifty-six patients with PR without evidence of GCA have been followed for a minimum of four years. Fifty-four have been treated successfully with 10 mg of prednisone a day or less. Only two patients required 15 mg. None have become blind or developed other complications of GCA and steroid side effects have been essentially absent. PR without clinical evidence of GCA can be safely treated with the small dose of steroids necessary to control symptoms as long as constant vigilance for signs of GCA is maintained.

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A New Technique for Resection of Gastric Polyps

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Abstract

Two problems created by a standard resection of a gastric polyp are an everted suture line and a radiographic defect which is difficult to interpret. With the use of the GIA Stapling Device, we have produced an inverted suture line with a permanently identifiable area of resection.

Standard resection of solitary benign gastric lesions creates an everted suture line and a deformity which is difficult to interpret radiographically. A technique is described utilizing the STAPLING apparatus that overcomes both these shortcomings.

Technique

At laparotomy, the gastrocolic ligament is widely opened and an anterior gastrotomy is performed to locate the gastric lesion (i.e. polyp or leiomyoma). The entire mucosal surface is inspected to identify other pathology. If the lesion is solitary and wedge resection will not comprise the pylorus or cardioesophageal junction, resection is accomplished. The tumor, with a margin of surrounding normal stomach, is grasped with BABCOCK clamps (full thickness) and elevated. The GIA Stapling Device (United States Surgical Corp.) is placed beneath the lesion and engaged, excising the specimen and leaving only an inverted suture (staple) line. A locking #3-0 chromic catgut suture is placed over the inverted resection line for hemostasis. The anterior gastrotomy is closed in the usual manner, followed by closure of the abdomen.

Discussion

The standard technique for resection of a solitary gastric lesion consists of a wedge resection of the portion of stomach with a two layer closure, everting the inner layer (1, 2). This method produces at least a theoretically undesirable situation with intramural dead space and the possibility of hematoma or abscess formation and subsequent suture line breakdown. The technique described avoids this problem by inverting the suture line, excising the lesion with a margin under direct vision, while markedly decreasing the operative time.

The greatest benefit of metallic staples in the area of resection is in long-term radiographic follow-up. A deformity is naturally created by any technique. Attempts at interpreting subsequent upper gastrointestinal series are ham-

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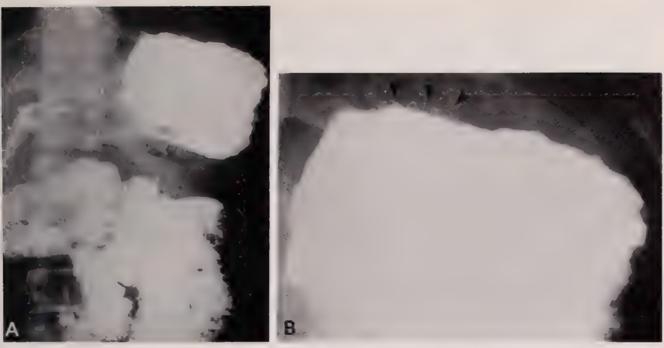

FIG. 1A. Area of surgical deformity localizing surgically created radiographic defect.
FIG. 1B. Staple line in area of resection (coned view).

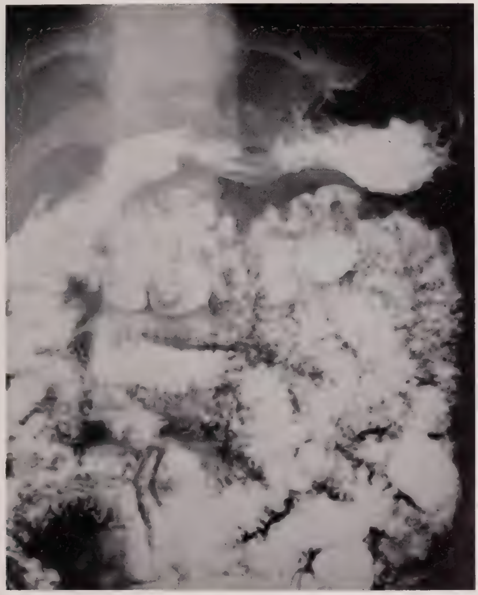

FIG. 2. Staples identifying area of resection on upper gastrointestinal series.

pered by the abnormality. A radiopaque staple line definitely localizes the area of prior surgery (Fig. 1A & 1B) and therefore provides a permanent marker for future barium studies (Fig. 2).

We have used the GIA Stapler for gastric wedge resection in five patients and found it simple and rapid, producing a technically preferable inverted suture line, and an identifiable defect on contrast radiography.

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Chronic Pain Exacerbated by Long-Term Narcotic Use in Patients with Nonmalignant Disease: Clinical Syndrome and Treatment

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Chronic pain in nonmalignant disease is a common disabling ailment and a vexing problem. Patients with chronic pain may suffer a number of complications of treatment, including addiction to narcotics. Although the major difficulty in pain management with narcotic analgesics lies in addiction, it has been thought that pain relief is generally obtainable with sufficiently high dosage. As patients with chronic pain have been followed in centers for the study and treatment of pain during the past several years, it has become evident that in some, elimination of the narcotic dose results in significant relief, not only of general symptoms related to addiction, but also of specific, focal pain symptoms, which had been exacerbated by the administration of narcotics.

In this study, the problem of chronic pain in nonmalignant disease complicated by iatrogenic narcotic addiction is presented in four patients. The clinical syndrome is analyzed and its treatment discussed.

Case Reports

Case 1. A 33-year-old man had an eight-year history of low back pain radiating to the right lower extremity following an auto accident. Two operations were performed in 1972 for removal of a herniated intervertebral disc on the right at L4/L5. In October, 1973, a myelogram revealed a "block" at L4 and a complete L4 laminectomy and L4-S1 fusion were performed. Subsequently there was relief of discomfort for seven months. In June, 1974, the low back pain recurred and repeat myelography demonstrated a "large defect at L4/L5," with an incomplete block. The region of the cauda equina at L4 was then explored. A pseudoarthrosis was seen at this level and the fusion mass was removed. A right L4/L5 foraminotomy was performed. The patient was free from pain for approximately two months when the pain gradually returned. Prior to admission on July 23, 1975, the patient was taking percodan, ten to twelve tablets daily.*

Physical examination revealed weakness to mild resistance in dorsiflexion of the right great toe. There was hypalgesia over the dorsum of the right foot. Straight leg raising was limited to 50° bilaterally.

Gradual narcotic withdrawal was undertaken and methadone 5 mg twice daily was ordered initially. Fluphenazine 1mg 3 times a day and amitryptyline 75mg at bedtime were added, and physiotherapy was initiated. The methadone dose was decreased and discontinued on the sixth

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* All drug administration is by mouth unless otherwise specified.

day of hospitalization. The patient showed marked improvement with minimal complaints of pain and an increasing proficiency in his physical exercises.

The patient was discharged on August 2, 1975 completely free of pain and on no medication. The discharge neurological examination was entirely within normal limits except for persistent weakness of the right great toe. The patient has remained pain free on no medication and has returned to work.

Case 2. A 52-year-old man was admitted to the Yale New Haven Hospital (YNHH) on June 15, 1975 with a six-month history of low back pain radiating to the left lower extremity. He had had a laminectomy, left L5/S1 with fusion, for a herniated intervertebral disc in 1959 and a second laminectomy, left L4/L5, for another herniated intervertebral disc in 1972. The patient also had a history of occasional episodes of depression. Immediate preadmission medication were desipramine 50mg at bedtime, codeine 60mg every 4 hrs, glutethimide 250mg 3 times daily and meperidine 50mg every 4 hrs.

Physical examination demonstrated moderate lumbosacral muscle spasm bilaterally. Back flexion was limited to 45° and extension to 10° with resultant pain in the left lower back. Straight leg raising was limited to 80° on the right, and to 30° on the left by pain radiating down the posterolateral aspect of the left iliopsoas, quadriceps and hamstrings. The left ankle jerk was absent. Hypalgesia was present over the dorsum of the left foot.

The patient was placed on bedrest and physical therapy. A myelogram demonstrated an irregular contour of the contrast column from the L3 to L5 levels. On the day of admission, acetaminophen 20 grains every 4 hrs as needed and Dalmane 30mg at bedtime was ordered. Following this the patient developed nausea, diarrhea, and generalized muscular aches with exacerbation of his low back pain. This lasted three days. On the second day of hospitalization, chlorpromazine 50mg 3 times daily was ordered. This was discontinued five days later and the patient's medication changed to fluphenazine 1mg 3 times daily and desipramine 50mg at bedtime. A marked decrease in pain occurred.

He was discharged on June 27, 1975 completely pain free on fluphenazine 1mg 3 times a day and desipramine 50mg at night. The only neurological deficit was an absent left ankle jerk. One week after discharge fluphenazine was discontinued. Two months later the patient had no pain and was conducting his routine daily activities. He continued to use acetaminophen as needed.

The patient remained pain free for six months at which time he experienced a recurrence of mild low back pain associated with stress at work and moderate depression. He presently takes no narcotics and continues his exercise regimen.

Case 3. A 40-year-old woman was admitted to YNHH on June 5, 1975 with a ten month history of pain in the neck and left arm. Treatment with cervical traction and a soft collar yielded transient relief. Cervical myelography was reported as normal. An electromyogram showed mild evidence of denervation of the muscles supplied by the C5-C6 nerve roots on the left. Three weeks prior to admission, her pain grew steadily worse. Preceding admission, her medications were diazepam, five 10mg tablets daily, and Percodan, 2 tablets every 3 hrs.

Physical examination demonstrated no reflex or sensory changes. There was mild weakness in flexion of the forearm and abduction of the arm on the left.

Gradual narcotic withdrawal was undertaken and methadone 5mg twice daily was ordered initially. Fluphenazine 1mg 3 times a day and amitryptyline 75mg at bedtime were added, and physiotherapy was initiated. The methadone dose was decreased and discontinued on the sixth day of hospitalization. The patient showed marked improvement with minimal complaints of pain and advanced progressively in her physical exercises.

Upon discharge, the patient was neurologically intact with no pain and receiving only acetaminophen. She has remained pain free and has resumed her usual occupation.

Case 4. A 43-year-old man was first admitted to YNHH on July 14, 1975 for evaluation of pain in the back radiating to both lower extremities, and in the left shoulder radiating to the hand. In April, 1972, a myelogram was reported to demonstrate a "defect" on the left at L4/L5, which was decompressed. There was minimal improvement. In October, 1972, the L4/L5 and L5/S1 intervertebral spaces on the left were reexplored, and a bilateral posterolateral fusion was carried out from L4-S1. No improvement in symptoms occurred. About this time, the patient was involved in an automobile accident with resultant neck pain. After conservative therapy had failed, the patient underwent an anterior discectomy of C6/C7 and a Cloward fusion in March, 1973. The neck pain persisted, and in December, 1973, anterior discectomies and fusion were performed at C4/C5 and C5/C6. Postoperatively, the pain was not relieved. In June, 1975, a "dorsal column" stimulator was placed at the cervical level with no pain relief. Medications included diazepam 10mg 3 times a day, levorphanol 4 tablets daily, and sodium amobarbital 100mg at bedtime. In the past, the patient had received morphine, meperidine, codeine, Percodan and Pantopon.

Physical examination revealed an increased lumbar lordosis and bilateral paraspinal muscle spasm. Straight leg raising on the right was 85° and 10° on the left, limited by back pain. Dorsiflexion, eversion and inversion of the left foot could be only performed against gravity, not resistance. The left great toe exhibited only a flicker of movement in extension. Hypalgesia was present over the dorsum and sole of the left foot.

Withdrawal from narcotics was begun, and the patient was placed on methadone 5mg every 6 hrs and flurazepam 30mg at bedtime. On the second day of hospitalization a mild abstinence syndrome was apparent with nausea, diarrhea, agitation and insomnia. On the next day, methadone was decreased and fluphenazine 1mg 3 times a day and amitriptyline 50mg at bedtime were ordered. The methadone was discontinued on the fifth day after admission. An exercise regime was started. The patient's symptoms improved, with pain reported only during exercise.

The patient was discharged to receive fluphenazine 1mg 3 times a day and flurazepam 30mg at bedtime. He experienced no pain. Two weeks later all medications were discontinued.

Two months after discharge, the patient fell at work and subsequently complained of incapacitating low back pain. Although the patient required no narcotics for pain relief, he remained out of work while litigation relative to his fall was pursued. After a brief hospitalization and treatment with non-narcotic analgesics, the patient was discharged, again with no pain.

Discussion

The use of narcotics in the management of chronic benign pain is controversial. With repeated daily administration tolerance as well as some degree of physical dependence develops. Often, after the resolution or remission of chronic pain, a residue of drug dependence replaces pain as the primary problem.

The tendency toward narcotic ingestion may be encouraged initially by the induction of euphoria or by the reduction of tension, pain and anxiety. Later the development of tolerance and dependence produces new tension, and the suppression of ensuing withdrawal symptoms further encourages drug use. Complaints of pain can be stimulated by the prescription of narcotic analgesics, which can act as positive reinforcers of the behavior that leads to their administration (1).

Narcotics are often consumed in amounts seemingly inappropriate for the nature and degree of identifiable organic pathology (2). Some investigators maintain that the majority of patients with chronic pain misuse whatever drugs they are given, and that a significant percentage abuse drugs regularly in spite of appropriate instructions from their physicians (3). In a study of one hundred consecutive patients referred for a complaint of pain, 95% were taking narcotics, 80% were taking psychotropic agents, over half were using antagonistic or incompatible drugs, and almost 90% were thought to have significant withdrawal symptoms (3, 4).

When patients who are iatrogenically addicted to narcotics become tolerant to a given dose or drug, a subtle withdrawal syndrome may periodically manifest itself. A prominent symptom of this withdrawal is pain. In our work involving patients with chronic pain, we have repeatedly made the observation that long-term narcotic use with resultant tolerance and withdrawal may often be associated with a marked increase in the original pain complaint (5). This is a sustained, focal pain syndrome of the same nature and distribution as the pain for which narcotics were initially prescribed. We have seen, not infrequently, that a clinician will mistake an exacerbation of pain associated with chronic narcotic administration as a continuance of organic disease rather than as a complication of narcotic therapy. An escalating, cyclic pattern of higher narcotic dose, followed by increased pain, treated with more narcotics inducing greater pain, and so on, often evolves. Surgery may even be recommended and performed.

It is important, therefore, to be cognizant of a group of patients with chronic pain, who develop tolerance and subtly withdraw from their narcotic analgesic and thus experience more pain on the basis of withdrawal rather than from progression of organic disease.

A detoxification program is one therapeutic approach to this problem. Detoxification from opiates can be done relatively rapidly, and when done carefully, does not threaten life (6, 7). Halpern (6) and Seres and Newman (7) have carried out detoxification programs involving drug substitution, stabilization and withdrawal in addicted patients with chronic pain. Following decreased drug intake and progressing to complete narcotic withdrawal, an improvement in the psychological and physical functioning of patients was noted. Significantly greater relief of pain was achieved with no narcotic than with high doses of narcotic and sedative drugs (6, 7). In our patients, we have found a similar detoxification method consisting of transient drug substitution with methadone and/or psychotropic agents to be very safe and effective (5, 8).

The complaint of pain may result from the action of a number of factors, and at any time, one or more may predominate (8). Two of our patients are pain free on no medication whatever. A third patient experienced a recurrent episode of depression six months after discharge which was associated with an exacerbation of his previous pain symptoms. However, his pain is presently well controlled with nonnarcotic analgesics. The fourth patient's pain recurred after a fall at work concerning which litigation was pursued. A patient may leave the hospital denying pain on no medication, but this does not mean that he is "cured" of pain. Although pain associated with narcotic addiction has been effectively treated by detoxification, it may recur upon another basis, i.e., depression, litigation, or progression of disease.

The indications for the surgical treatment of pain are not well defined. It is important to recognize that an increase in narcotic dose in a patient suffering with chronic pain is often more suggestive of drug tolerance and dependency rather than progression of a surgically relievable disorder. As is well known, attempted surgical therapy for pain is almost uniformly unsuccessful in a patient addicted to narcotics. Three of our four patients underwent multiple surgical procedures for persistent pain without obtaining significant or sustained relief.

The results of this study indicate that an appropriate first approach for the treatment of chronic pain of nonmalignant origin in patients iatrogenically addicted to narcotic analgesics consists in the withdrawal of such narcotics in a hospital setting permitting close observation. It should not be assumed that the complaint of pain will always increase under these circumstances. In fact, it may decrease, and surgical alternatives need not be considered. If on the other hand pain complaints persist, then the remaining signs and symptoms may be evaluated without the complicating features of narcotic addiction, and a rational evaluation of the indication for and against further treatment, including surgery, may be obtained.

The reduction in pain noted in these reported cases need not only be due to narcotic withdrawal. Several factors including physical exercise, the hospital environment, psychological reinforcement and other considerations may be of significance.

Our clinical experience demonstrates that chronic pain can be exacerbated by long-term narcotic therapy as tolerance and dependency develop, and that the occurrence of this complication is often not recognized. We suggest, therefore, that withdrawal from narcotics in the iatrogenically addicted patient with chronic pain can be an important factor in its reduction, and also, that drug detoxification should precede planned surgical intervention for the relief of pain inasmuch as equivalent relief may be obtained by withdrawal alone.

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Cytopathic Effects of a Virus-Like Agent Isolated in Lupus Erythematosus: Studies in 3 Cases of Low-Grade Severity*

SYLVAN E. MOOLTEN, M.D., ALICE M. SILVER, AND MIKLOS MIHALYFI

Abstract

Results of earlier studies in severe cases and the present studies in milder cases support the proposition that lupus erythematosus is associated consistently with a distinctive type of blood-borne virus-like agent transmissible in chick embryos. The agent was shown capable of inducing characteristic cytopathic changes in normal human leukocytes in vitro consisting of a spectrum ranging from tart cells and pseudo-LE cells to typical LE cells. The affinity of the agent for red blood cells was demonstrated in the form of virus-type hemagglutination and in the sensitization of the red blood cells of lupus patients in vivo to the agglutinating action of the homologous antiserum. These observations suggest that the interactions of this agent with blood cells underlie its dissemination within the body, the LE cell phenomenon in vitro, and some of the hematological complications of the disease.

The mystery that surrounds the etiology of lupus erythematosus has had special fascination for investigators and clinicians alike. Is it an "autoimmune disease" or is it an "infection", in particular a slow virus infection? In 1948 Bergamasco inoculated chick embryos with pooled samples of blood of four patients with SLE and reported the presence of a virus of hemagglutinating type (1). In 1965 Murphy et al (2) described a virus-like agent isolated from bone marrow and morphologically similar to known viruses in a child with SLE incidentally to a study of acute leukemia in children. Subsequently Grishman et al (3), Fresco (4), Györkey et al (5), Norton et al (6), among many other investigators, described cytoplasmic microtubular structures, possibly viral in origin, in glomerular endothelium, lymphocytes, muscle and other tissues. In the last few years the concept of SLE as a virus infection has gained further headway through studies purporting to implicate Type C viruses in its pathogenesis (7–9), and the demonstration of Type C RNA viruses in NZB mice (10–12), a strain that manifests virtually all the features of SLE in man.

Our own interest in the possible viral etiology of LE had its origin in 1950, when we isolated a transmissible virus-like agent from the blood of two patients with SLE who were part of a series under investigation for the role of blood-borne viruses in acute hemolytic anemia and autohemagglutination (13, 14).

Our further studies in this field were directed chiefly to studies of interaction of the SLE agent with red blood cells and leukocytes (15).

The affinity of certain viruses for the red cell had been known since 1941 as an in vitro phenomenon useful in virologic diagnosis. Shwartzman later pro-

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posed that the same phenomenon may play a role in the blood-borne transport of viruses within the living organism (16).

Our use of blood as inoculum for isolation of virus was based on the idea that recirculation of red cells repeatedly through virus-infected tissues enables them to accumulate a relatively large concentration of virus material upon their surface. Hemolytic anemia may then result either from the direct action of virus on red cells or indirectly through immune complexes of viral antigen and antibody (Coombs-positive hemolytic anemia) (13).

In the initial phase of our work* we isolated virus-like agents in 8 out of 12 trials. Standard hemagglutinin inhibition tests revealed close immunological relationship of several isolates tested with specific antiserum. In the next phase** we isolated the agent in 43 out of 87 trials and in 8 of the cases on 2 or more occasions during periods ranging from 4 months to 6 years (15).

Studies in Lupus Erythematosus of Low-Grade Severity:

The present report summarizes more recent studies having as their objective the demonstration of the same or similar type of virus-like agent in cases of chronic SLE of low-grade severity and a case of chronic discoid lupus erythematosus. Although we employed the same techniques as in our earlier studies dealing with acute and subacute cases of systemic lupus erythematosus, we rarely obtained evidence of vigorous multiplication of an agent in chick embryos in the form of virus-type plaques or embryo death, but observed instead merely hyperemia and edema of the chorioallantoic membrane and sluggishness of embryonic movements. Accordingly we resorted to the following indirect methods for demonstrating the specific relation of the agent to the disease:

1. Examination of cytopathic effects in normal leukocytes in vitro by allantoic fluid of inoculated chick embryos.
2. Tests of agglutinability of red blood cells by immune serum in cases of proved SLE.
3. Infectivity neutralization tests in chick embryos with immune serum.

In a few instances we permitted infected chicks to hatch. These showed clearly identifiable abnormalities of the feet, recalling observations of Warren et al (17) in chick embryos inoculated with synovial tissue of human patients with rheumatoid arthritis.

Methods

Isolation of LE Agent by Chick Embryo Inoculation: Samples of venous blood of patients with lupus erythematosus were drawn aseptically and allowed to clot at room temperature. After clot retraction had begun the samples were kept at refrigerator temperature (4°C) until the following morning. The inoculum consisted of serum with a small amount of red cells in approximately 0.5 percent suspension, preferably cells that had become freed spontaneously from the clot and settled to the bottom of the tube. The material was treated with penicillin and kanamycin in final concentrations of 100 units per ml. and inoculated chorioallantoically in 0.1 ml. amounts in 4 to 6 11-day-old chick embryos* by the method of Beveridge and Burnet (18).

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* 1950–1956 (S.E. Moolten and Ellen Clark)

** 1961–1969 (S.E. Moolten and M. Mihalyfi)

The eggs were incubated at 36°C and candled twice daily for evidence of infection indicated by diminution or cessation of embryonic movements. Material for study was harvested generally at 72 hours. In some instances the eggs were permitted to hatch.

When the eggs were opened the allantoic fluid was aspirated aseptically for passage into other embryos and for tests for the presence of viral-type hemagglutinins. The chorioallantoic membranes were excised carefully and spread in saline in a Petri dish to permit inspection for the presence of viral-type foci. To rule out bacterial growth, cultures of egg fluid, embryonic stalk, yolk sac, and embryonic organs were made in standard aerobic and anaerobic culture media together with examinations of stained smears.

Passages of the agent were maintained in most instances by chorioallantoic inoculation and, on occasion, by allantoic inoculation, the inoculum consisting of 0.1 ml. amounts of pooled egg fluid or the fluids of a particular embryo.

Tests of Cytopathic Effects: Buffy coat material for cytopathic studies was obtained from venous blood of several healthy laboratory technicians. The blood sample (10 ml. in each study) was drawn aseptically into a tube containing 1 ml. of freshly made sodium citrate solution (3.8 percent).

Allantoic fluid in a proportion of 1:2 was added directly to the citrated blood, the contents of the tube were shaken, and the mixture was incubated at room temperature for two hours. Following this the tube was centrifuged at 1000 r.p.m. for 10 minutes. The supernatant plasma was drawn off by pipette with care to avoid agitation of the buffy coat. The buffy coat with a small amount of remaining plasma was then drawn off separately into a Wintrobe hematocrit tube and centrifuged lightly to achieve better separation of leukocytes, plasma and red cells. The buffy coat layer obtained thereby was drawn by pipette and expelled in small drops upon each of several clean slides. Smears were made in the usual manner for routine blood smears and stained with Wright's stain. Two slides of each buffy coat were mounted and inspected under high dry magnification. All cells were examined and cells showing changes were classified as follows:

LP Cells: Polymorphonuclear leukocytes and monocytes containing engulfed leukocytes undergoing lysis**.

Tart Cells: Polymorphonuclear leukocytes and monocytes containing engulfed nuclear masses showing distinct chromatin.

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* The embryonated eggs were of certified stock obtained from two sources, Vincent Darago and the Department of Poultry Pathology of the Rutgers University School of Environmental Science. In the experience of one of us (M.M.) during several years of virus research at the Institute of Microbiology, Rutgers University, and within our own group, these eggs have uniformly failed to show the presence of avian viruses or mycoplasmas.

** LP: Lysis-phagocytosis.

Leukocytes containing engulfed intact leukocytes showing no appreciable lysis were also enumerated.

One of us (A. S.) was designated principal observer of the cytopathic effects throughout the entire study and after practice attained a high degree of accuracy and consistency in grading the relative number of cells in each category on a scale of 0 to ++++.

Parallel studies were performed with passaged allantoic fluid of embryos inoculated with blood samples obtained from healthy laboratory technicians, from the virologist (M. M.), and from a patient with Hodgkin's disease and a patient with infectious mononucleosis. To exclude the possible cytopathic effect of latent avian viruses we tested allantoic fluid from normal (uninoculated) eggs simultaneously with test allantoic fluid.

Tests of Cytopathic Effects of Known Viruses: In order to evaluate the general applicability of the buffy coat technique in the study of viruses, we tested the following strains of known viruses for cytopathic effects in the same manner as the LE agent:

Fowl Pox (field isolate)*
Infectious laryngotracheitis (standard strain)*
Avian encephalomyelitis (DeKalb strain)*
Avian infectious bronchitis (egg-adapted Beaudette strain)*
Eastern equine encephalitis (field isolate)*
Newcastle disease virus (BK strain)*
Newcastle disease virus (H strain, RO strain)**
Influenza virus (PR8, WSN, and Japanese strains)**

Production of Immune Serum: Healthy female rabbits weighing approximately 2.5 kg. were given two intramuscular injections of freshly harvested infected egg fluid (passage #19 of the LE-Ran strain)*** emulsified in Freund's adjuvant in 2 ml. doses at an interval of three weeks. One week after the second intramuscular injection the animals were bled to determine the antibody titer of their serum. Thereafter they received booster doses of 1 ml. of untreated egg fluid at monthly intervals. Blood samples (usually 20–30 ml.) were drawn as required and the serum was stored in the refrigerator for future use.

Before use each rabbit antiserum was shaken gently with successive additions of small amounts of washed normal human red blood cells of all available types in the hospital's blood bank (approximately 0.1 percent suspension) to remove heterospecific and blood group-specific antibodies, allowed to stand for several hours or overnight in the refrigerator, examined for red cell clumping, and cleared by centrifugation at 2500 r.p.m. When no trace of agglutination of normal red cells could be demonstrated the final suspension was cleared by centrifugation at 2500 r.p.m., the serum inactivated by heating to 56°C for 30 minutes, centrifuged again at 2500 r.p.m. until it was crystal clear, and checked for sterility.

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* Supplied by Dr. David C. Tudor, Research Professor of Animal Pathology, College of Agriculture and Environmental Science, Rutgers University.

** Supplied by Dr. Robert W. Simpson, Associate Professor of Virology, Institute of Microbiology, Rutgers University.

*** Isolated from patient "Ran"

The antibody titer of immune serum was determined in infectivity neutralization tests of the active agent. Twelve embryos were inoculated with infected allantoic fluid mixed with the serum in serial dilutions to 1:100. The mixtures were allowed to stand 30 minutes in the refrigerator before inoculation of the embryos. Control sera treated in similar manner included normal human serum, normal rabbit serum, and immune rabbit serum against agents isolated from blood of patients with Hodgkin's disease (15) and infectious mononucleosis.

Tests for Neutralization of Cytopathic Effects: Infected allantoic fluid was mixed with specific immune serum in varying proportions and incubated with buffy coat leukocytes for two hours. Smears were made in the usual way and examined for cytopathic effects. Control tests were run with untreated allantoic fluid and with allantoic fluid mixed with normal rabbit serum.

Tests for Virus-Like Antigen Adsorbed to Red Cells (Method of Moolten and Clark) (14). A sample of the patient's venous blood was allowed to clot at room temperature. Red cells freed from the clot were washed lightly and then added in 2 percent suspension in saline to a row of serial two-fold dilutions of each of the immune sera and control normal rabbit serum of the panel. The

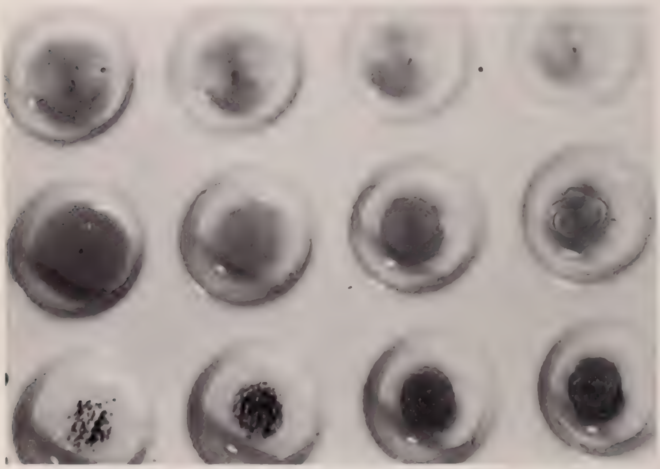

FIG. 1. Serologic identification of antigen-coated red cells by specific antiserum:
Normal RBC + immune serum (upper row)
Patient's RBC + normal rabbit serum (middle row)
Positive agglutination test (1:20) with patient's RBC + specific serum (bottom row)

tubes were thoroughly shaken, left at room temperature for 2 hours, (or overnight in the refrigerator), and then examined for specific agglutination of antigen-antibody type, stable at 37°C and not dispersed by vigorous tapping (Fig. 1).

Results

During a period of approximately one year we examined blood samples of 11 patients with chronic lupus erythematosus for evidence of replication of LE agent in embryonated eggs and for white cell cytopathic activity in vitro. Of these, 10 gave positive results for LP cells after serial passage in eggs. At times it was difficult to ascertain whether lysis of the inclusion body would warrant classification as an LE cell, but generally, as shown in the illustration (Fig. 2) the inclusion body lacked complete homogenization and tended to show denser

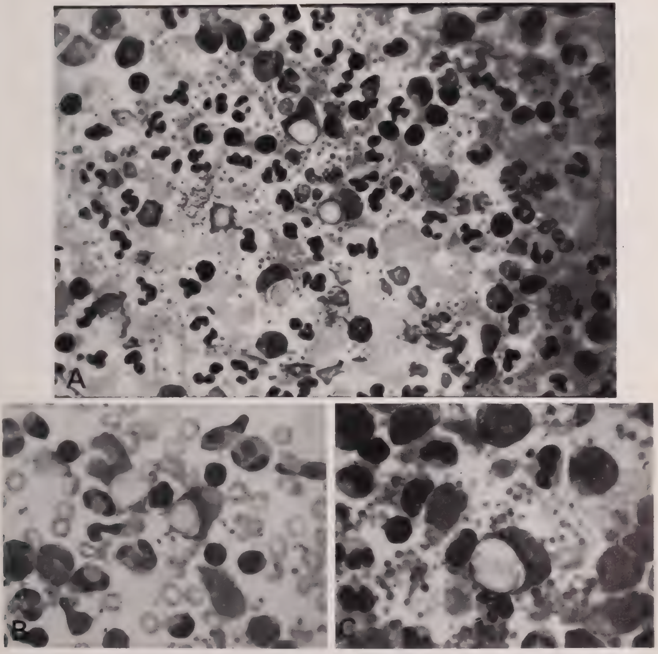

FIG. 2A. Cytopathic effects (LP cell phenomenon) induced in normal leukocytes by agents isolated from patient with chronic LE (passage fluid of infected chick embryo). B,C Photomicrographs (enlarged) showing LP phenomenon in greater detail

color in its periphery. In these respects the LP cells conformed rather to the designation of pseudo-LE cells (19) (or "Type B" cell of Heller and Zimmerman (20)). These were differentiated from tart cells by the fact that the chromatin pattern of the inclusion body was largely dissipated. We selected the isolates in 3 cases (Ran, LC and CP) for an extended series of observations.

Ran: female, 47, was treated with corticosteroids for SLE since age 32. She had splenectomy for Coombs-positive hemolytic anemia at 39. She developed thrombophlebitis complicated by multiple pulmonary emboli at 42. Subsequently, LE cell tests became negative for LE cells but revealed persistent marked erythrophagocytosis. Antiserum produced in rabbits inoculated with the LE agent isolated from her blood (strain LE-Ran) by our standard technique yielded high titers of neutralizing antibodies and agglutinated her red blood cells strongly in high dilution.

LC: Female, 39, had recurrent pleurisy and arthritis since age 23 and unexplained anemia and leukopenia since age 26. On her last hospital admission she was treated for pneumonia; chest x-ray on recovery showed patchy linear infiltrates in both lower lobes. The sedimentation rate (Westergren) was 102–122 mm. in 1 hour. The hemoglobin was 10.5 Gm., hemotocrit 33, white cell count 2,200, neutrophiles 38 percent. Tests for LE cell factor, antinuclear factor and rheumatoid factor were all positive. Tests for agglutinability of her red cells by immune serum against the LE agent (LE-Ran) were positive in significant dilution.

CP: male, 18, developed chronic discoid lupus erythematosus confined to the right side of the scalp and forehead at age 13, followed by "butterfly" eruption on the cheeks. Diagnosis was confirmed by biopsy; LE cell tests were negative. At one time he had a severe skin "reaction" on the back of the neck following exposure to sun in Switzerland. Since then he has been in good general health. The hemoglobin at present is 16.4 Gm., hematocrit 49, white cell count 6,000 with normal differential, sedimentation rate 2 mm. in one hour. His skin is free of eruption except for slight scaly patches on the scalp. Red cell agglutination test with immune serum against the LE agent (LE-Ran) was positive in significant dilution.

As Table I shows, the activity of the LE agent in producing LP cells was maintained through numerous serial passages, in one case (LE-Ran) for 95 passages, and in another case (LE-LC) for 88 passages, although in both cases in progressively diminishing degree. Weak cytopathic activity appeared again in the LE-Ran strain in its 123rd passage. Tart cells were much more abundant when there were LP cells than in their absence. The LE agent isolated in the case of chronic discoid lupus (LE-CP) yielded positive results of the same order of intensity as observed in the cases of systemic lupus.

Tables II and III list the results of chick embryo passage of blood samples in 5 cases of Hodgkin's disease and one case of infectious mononucleosis and of samples of allantoic fluid from uninoculated eggs of each of the last 13 batches employed in the study. None of the control tests yielded a positive LP reaction. Tart cells were not uncommon in the control tests, but their incidence was relatively small compared with that observed when there were LP cells.

TABLE I

Cytopathic Tests of Agents Isolated in 3 Cases of Lupus Erythematosus

Donor of Normal Blood Sample	Egg Passage #	LE-Ran Isolate				Egg Passage #	LE-LC Isolate				Egg Passage #	LE-CP Isolate			
		LP Cells		Tart Cells			LP Cells		Tart Cells			LP Cells		Tart Cells	
		Polys	Monos	Polys	Monos		Polys	Monos	Polys	Monos		Polys	Monos	Polys	Monos
JW	19	+	++	++++	++++										
JL	21	+	+++	++++	++++										
JW	24	+	++	++	++++										
JB	25	0	+	++	++++										
GC	27	0	+	0	++										
JW	29	+	++++	++	++++										
GC	31	+	+++	0	++++										
GC	33	0	+	0	++										
JL	35	0	+++	+	++										
GC	37	0	++	+	++										
LO		+	+	++++	++++										
JW		0	++	++	+++										
LO	45	+++	++	++++	++										
JL	49	0	++	++	++++	7	0	+++	++	+++	4	+	+++	++	+++
LO		++	+	+++	++		+	0	++	+		++	+	++++	++
JW		+	++	++	+++		+	++++	++	++++		0	++	+	++
EK	50	++	++	++++	++++										
GC	51	+	++	++	++++	9	+	+++	+++	++++	6	+	++	++	++++
JW	59	+	++	++	+++						14	+	++	++	++++
DB		+	++	+	+++							+	++	++	++++
JS		++	++	+++	+++							++	+	++++	+++
GC	64	0	++	+	++										
GC	95	0	+	+	++										
GC	117	0	0	0	+										
JL	123	0	+	+	+										
GC	127	0	0	0	++	84	0	+	+	+++					
JW	129	0	0	+	+										
JL	131	0	0	0	++	88	0	+	0	+					

Ran, LC; Patients with Chronic Systemic Lupus Erythematosus. CP: Patient with chronic Discoid Lupus Erythematosus. (Passages made twice weekly).

TABLE II

*Cytopathic Tests in Cases of Hodgkin's Disease**

Donor	Egg Passage #	HD-HW				Egg Passage #	HD-MD				Egg Passage #	HD-MF			
		LP Cells		Tart Cells			LP Cells		Tart Cells			LP Cells		Tart Cells	
		Polys	Monos	Polys	Monos		Polys	Monos	Polys	Monos		Polys	Monos	Polys	Monos
JW	10	0	0	+	+	10	0	0	0	++	10	0	0	0	+
JL	12	0	0	0	+	12	0	0	0	+	12	0	0	0	0
JW	14	0	0	++++	++++	14	0	0	0	+	14	0	0	0	0
JB	16	0	0	0	++	16	0	0	0	++	16	0	0	0	++
GC	18	0	0	0	+	18	0	0	0	0	18	0	0	0	0
JW	20	0	0	0	+	20	0	0	0	0	20	0	0	+	+
GC	22	0	0	0	+	22	0	0	0	+	22	0	0	0	++
GC	24	0	0	+	+	24	0	0	0	+	24	0	0	0	+
JL	26	0	0	0	+	26	0	0	0	++	26	0	0	0	0
LO	36	0	0	++	+	36	0	0	+	+	36	0	0	+	+
GC	42	0	0	0	++						42	0	0	+	+
GC	55	0	0	0	+										
GC	107	0	0	0	++										
JL	121	0	0	0	+										

Donor	Egg Passage #	HD-CT				Egg Passage #	HD-DUM			
		LP Cells		Tart Cells			LP Cells		Tart Cells	
		Polys	Monos	Polys	Monos		Polys	Monos	Polys	Monos
JW	12	0	0	0	+	10	0	0	0	+
JL	14	0	0	+	+	12	0	0	+	++
JW	16	0	0	0	0	14	0	0	0	+
JB	18	0	0	0	+	16	0	0	0	+
GC	20	0	0	+	+	18	0	0	0	+
JW	22	0	0	0	+	20	0	0	+	+
GC	24	0	0	0	+	22	0	0	0	+
GC	26	0	0	0	+	24	0	0	0	+
JL	28	0	0	0	++					
LO	38	0	0	0	+					
JL						42	0	0	+	+

* Tests run simultaneously with tests listed in Table I.

TABLE III

*Cytopathic Tests in Case of Infectious Mononucleosis: Tests of Normal Chick Embryos**

Donor	Egg Passage #	IM-TRO				Egg Passage #	D-Eggs			
		LP Cells		Tart Cells			LP Cells		Tart Cells	
		Polys	Monos	Polys	Monos		Polys	Monos	Polys	Monos
JW	16	0	0	0	+					
JL	18	0	0	0	+					
JW	20	0	0	0	0					
JB	22	0	0	0	++					
GC	24	0	0	0	++					
JW	26	0	0	0	0	4	0	0	0	0
GC	28	0	0	0	0	6	0	0	0	0
GC	30	0	0	+	+	8	0	0	0	+
JL	32	0	0	0	0	10	0	0	0	+
LO	42	0	0	0	+	20	0	0	+	++
GC	48	0	0	0	++	26	0	0	0	+
JW						0	0	0	0	0
DB						0	0	0	0	0
JS						0	0	0	0	+
GC	61	0	0	0	++	0	0	0	0	0
GC						0	0	0	0	+
JW						0	0	0	0	+
JL						0	0	0	0	+

TRO: Case of Infectious Mononucleosis. D-Eggs: Darago stock eggs.

* Tests run simultaneously with tests listed in Table I.

Table IV lists the results of tests of chick embryo passage of blood samples from 5 of the laboratory technicians employed as donors of buffy coat.

In the case of one of these donors (L.O.) a weakly positive LP reaction appeared on the 18th passage of a second inoculum but not subsequently. Although classed as healthy, this person had a history of rheumatoid arthritis beginning in childhood and at the time of this study had a positive RA test but no symptoms or laboratory evidence of SLE. All tests of the other donors were completely negative for the LP reaction.

Two strains of Newcastle disease virus (strain BK and strain H) tested against buffy coat leukocytes yielded a weakly positive result for LP cells. All other virus strains tested gave negative results for LP cells (Table V). Tests with avian bronchitis virus yielded a peculiar type of inclusion vaguely suggestive of the LE cell (Fig. 3); however the inclusion appeared to be derived from cytoplasmic or platelet material rather than whole cells or nuclei. Phagocytosis of intact leukocytes by other leukocytes and erythrophagocytosis were not uncommon findings in tests with the 3 strains of Newcastle disease virus (H, RO, BK) and with the 3 strains of influenza virus (Fig. 4), and occurred also in several tests with the LE agent. Leukophagocytosis was observed less commonly in tests with passage material of healthy donors.

Results of tests of the capacity of immune rabbit serum to neutralize the cytopathic activity of the LE agent in vitro are tabulated in Table VI. The immune serum produced against the LE-Ran agent (passage #64) neutralized LP activity of the same strain (passage #123) and LP activity of two separate strains of LE agent isolated from another patient (LE-LC_1, passages #84 and #88, and LE-LC_2 passage #9). Normal rabbit serum had no neutralizing power.

TABLE IV

Cytopathic Tests of Passage Material from Healthy Subjects

		C-JW						C-MM						C-LO			
Donor	Egg Passage #	LP Cells		Tart Cells		Donor	Egg Passage #	LP Cells		Tart Cells		Donor	Egg Passage #	LP Cells		Tart Cells	
		Polys	Monos	Polys	Monos			Polys	Monos	Polys	Monos			Polys	Monos	Polys	Monos
JL	16	0	0	0	0	JL	13	0	0	0	+	JW	13	0	0	+	+
GC	6*	0	0	0	+	GC	6*	0	0	0	+	JL	6*	0	0	+	+
GC	10	0	0	0	0	JW	10	0	0	0	+	GC	10	0	0	0	0
SM	16	0	0	0	0	SM	16	0	0	0	0	EU	16	0	0	0	0
JL	18	0	0	0	0	JL	18	0	0	0	0	JW	18	+	+	++	+++
GC	24	0	0	0	0	GC	24	0	0	0	+	JW	24	0	0	+	+
JL	26	0	0	0	+	JL	26	0	0	0	+	JL	26	0	0	0	+
JW	30	0	0	0	+	JW	30	0	0	0	0	JL	30	0	0	0	+
JW	48	0	0	0	0	JW	48	0	0	+	++	JW	48	0	0	+	+

		C-GC						C-JL						C-D Eggs			
Donor	Egg Passage #	LP Cells		Tart Cells		Donor	Egg Passage #	LP Cells		Tart Cells		Donor	Egg Passage #	LP Cells		Tart Cells	
		Polys	Monos	Polys	Monos			Polys	Monos	Polys	Monos			Polys	Monos	Polys	Monos
JW	13	0	0	0	0	JW	13	0	0	0	0	JL	0	0	0	0	+
JL	6*	0	0	0	+	GC	6*	0	0	0	+	JL	0	0	0	0	+
JW	10	0	0	0	+	JW	10	0	0	0	0	JW	0	0	0	0	0
EU	16	0	0	0	0	EU	16	0	0	0	0	EU	0	0	0	0	0
JW	18	0	0	0	0	JW	18	0	0	0	0	JW	0	0	0	0	0
JW	24	0	0	0	+	JW	24	0	0	0	0	GC	0	0	0	0	+
JW	26	0	0	0	0	JW	26	0	0	0	+	JW	0	0	0	0	+
JL	30	0	0	0	0	JL	30	0	0	0	+	JW	0	0	0	0	0
JW	48	0	0	+	++	JW	48	0	0	+	++	JW	0	0	0	+	+

* Second sample. JW, GC, JL: Normal Subjects. LO: Laboratory technician with history of rheumatoid arthritis; RA test positive. MM: Virologist. C-D Eggs: Egg fluid from batch of Darago stock eggs used on same date.

TABLE V

Tests of Known Viruses for Cytopathic Effects on Normal Leukocytes In Vitro

	Donor	LP Cells		Tart Cells	
		Polys	Monos	Polys	Monos
Veterinary Viruses					
Equine Encephalitis	JW	0	0	0	0
Avian Bronchitis	JW	0	0	+	++
Avian Bronchitis	JW	0	0	0	+
Newcastle Disease (BK)*	JN	+	0	+	+
Newcastle Diseae (H)	JN	0	+	+	+
Newcastle Disease (RO)*	JN	0	0	0	+
Epidemic Tremor	JW	0	0	0	+
Laryngotracheitis	JW	0	0	0	0
Pigeon Pox	JW	0	0	0	0
Canary Pox	JW	0	0	0	0
Influenza Viruses					
Influenza (Jap)	JW	0	0	0	+
Influenza (PR 8)	JW	0	0	0	+

* Dilution 1:100.

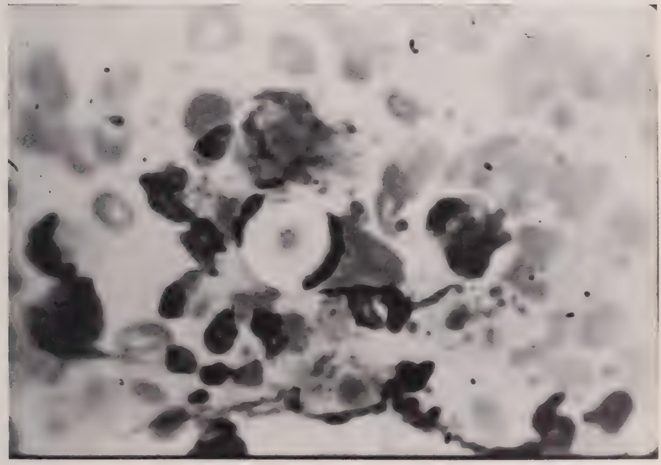

FIG. 3. Cytopathic effect of avian bronchitis virus.

Tests with immune serum produced against the LE agent (LE-Ran passage #19) agglutinated red cells of 11 out of 12 patients with proved SLE, all tests with other immune sera and with normal rabbit serum being negative. Despite the small size of this series, the results of these tests suggest that the LE-Ran

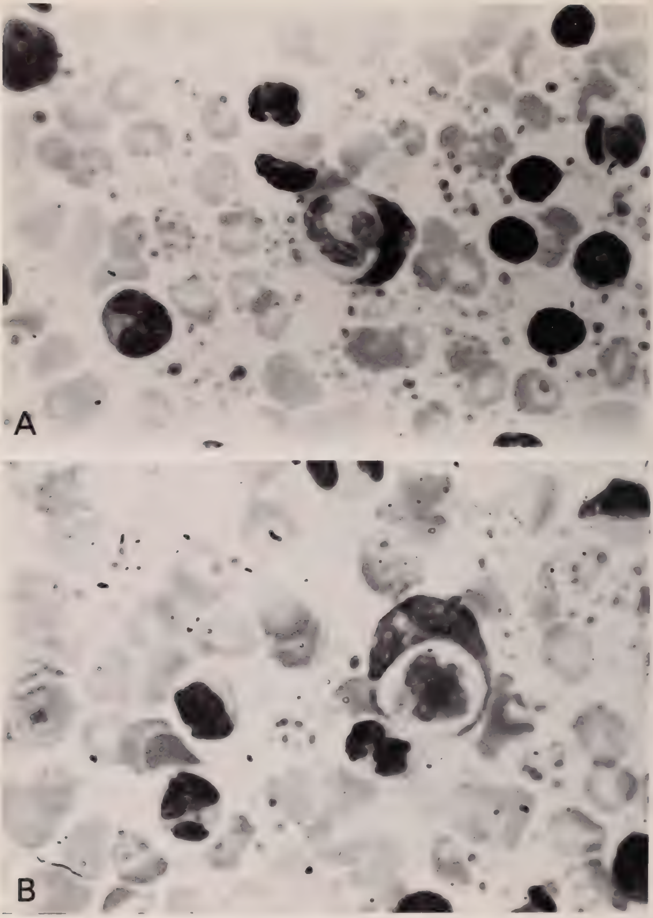

FIG. 4. A. Leukophagocytosis induced by influenza virus. B. Leukophagocytosis and partial lysis induced by Newcastle disease virus.

TABLE VI

Tests for Neutralization of Cytopathic Effects by Immune Serum

Donor	Strain	Passage #	Untreated Allantoic Fluid				Allantoic Fluid +Normal Rabbit Serum				Allantoic Fluid + Immune Rabbit Serum			
			LP Cells		Tart Cells		LP Cells		Tart Cells		LP Cells		Tart Cells	
			Polys	Monos	Polys	Monos	Polys	Monos	Polys	Monos	Polys	Monos	Polys	Monos
JL	JE-Ran	123	—	—	—	—	0	+	+	++	0	0	0	0
GC	LE-LC$_1$	84	0	+	+	+++	—	—	—	—	0	0	0	++
GC	LE-LC$_2$	9	0	+	0	+++	—	—	—	—	0	0	+	++
JL	LE-LC$_1$	88	0	+	0	+	—	—	—	—	0	0	0	+

Immune Serum: Produced by inoculation of rabbits with LE-Ran strain (passage #64)

TABLE VII

Red Cell Agglutination with Immune Sera against Virus-like Agents Isolated in cases of Systemic Lupus Erythematosus.

	Period of Study	Positive Tests	Total Tests	Per Cent Positive
Hodgkin's Disease	1950–1953	0	95	
	1965–1968	0	178	
			273	0
Leukemia, Lympho Sarcoma	1950–1953	0	33	
	1965–1968	0	145	
			178	0
Carcinoma	1950–1953	0	20	
	1965–1968	0	51	
			71	0
Systemic Lupus Erythematosus	1950–1953	34	60	
	1965–1968	11	41	
		45	101	44.4
Infectious Mononucleosis	1950–1953	0	58	
	1965–1968	0	28	
			86	0
Normal Controls; Other Diseases	1950–1953	0	271	
	1965–1968	0	124	
			395	0

strain of lupus agent possessed higher antigenicity for rabbits than the strains employed in the 1950–1953 series (34 positive results in 60 tests) or the 1965–1968 series (positive results in 41 tests), as indicated in Table VII.

Discussion

The results of this investigation confirm our earlier studies which implicate a blood-borne virus-like agent in a significantly high proportion of cases of SLE. Among its characteristics was the action of the "LE agent" on erythrocytes, manifested in virus-tupe hemagglutinins and in vivo sensitization of the erythrocytes of SLE patients to agglutination by homologous (anti-LE agent) immune serum. In the earlier studies, which were concerned with acute and subacute forms of SLE, the "LE agent" produced viral-type plaques in chick embryos or chick embryo death and induced changes in human leukocytes in vitro indistinguishable from the LE cell phenomenon (14, 15). In the present studies of relatively mild, chronic forms of LE, including chronic discoid LE, the agent produced less severe disease in chick embryos and less intense lysis and phagocytosis of normal leukocytes in vitro. In further contrast to the more vigorous "LE agent" isolated in earlier studies, in which as little as 0.1 ml. of infected allantoic fluid incubated with 10 times its volume of buffy coat was sufficient to induce cytopathic changes including typical LE cells, the LE agent isolated in the present studies produced significant cytopathic effects only when a much larger volume of the infected allantoic fluid was incubated with a comparatively small number of leukocytes. These effects, comparable to pseudo-LE cells, were with rare exceptions lacking in all control tests*.

It may be premature to regard the cytopathic changes observed with the "LE agent" following such brief incubation with normal leukocytes as simply the extension of the principle of virus cytopathogenicity such as observed in tissue culture or leukocyte culture. One must consider the possible intervention also of serum complement nonspecific lytic factors, or immune complexes formed by a union of the LE antigen with specific or group-related antibodies.

Despite the clearcut differences in cytopathic action between the "LE agent" and the other agents tested in this study, it would be foolhardy at this stage to characterize our method as a diagnostic tool for detecting a specific virus.

When we compared the results of tests with several veterinary viruses and influenza virus we observed cytopathic changes in the exposed leukocytes that were also unmistakably the result of viral activity. In the case of Newcastle disease virus these effects included a weakly positive LP reaction (lysis and phagocytosis of leukocytes). We observed also phagocytosis of intact leukocytes without lysis in the case of Newcastle disease virus and influenza virus, and lysis and phagocytosis of cytoplasmic or platelet material in the case of the virus of infectious avian bronchitis.

In an earlier study** in which we employed the same procedures as in our lupus cases, chick embryo inoculation of samples of maternal blood or cord blood in 8 cases of unexplained recurrent stillbirth or neonatal death also revealed the presence of virus-like agents. Allantoic fluid of these embryos induced formation of tart cells and, in some instances, LP cells when incubated with normal leukocytes. The blood serum of the affected mothers induced similar changes when incubated with normal leukocytes and their red blood cells were agglutinated by the homologous immune serum. None of these subjects had clinical or other manifestations of lupus erythematosus.

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* In preliminary trials in the fall of 1969 we tested 6 tubes of blood shipped by air freight from the University of Vancouver, Canada, by Dr. Denys K. Ford. Of the 6 samples, 2 were listed as controls from healthy persons, the remainder from patients with SLE. All yielded positive results. We are unable to explain the positive results in the two control specimens. In all subsequent studies performed on blood samples of healthy subjects working in our own area no false positives were obtained.

** Unpublished studies, 1950–1956 (S. E. Moolten and Ellen Clark).

The results obtained by us in these limited explorations of virus-leukocyte interaction emphasize the need for further study under suitably controlled conditions to confirm their validity and the general applicability of these methods in virology. It will be important also to determine the extent to which these in vitro phenomena have their counterpart in vivo as a manifestation of viral infection. The affinity of many viruses for red blood cells, expressed in the form of viral hemagglutinins and hemolysins, is exploited now as part of standard virologic technique in the laboratory, yet the role of virus-red cell interaction in the pathogenesis of certain types of hemolytic anemia had not been considered, prior to our publications in 1952 and 1953 (13, 14, 21).

Several compelling hints of the role also of virus-leukocyte interaction in viral infection are provided by such examples as the leukopenia of influenza (22), the leukopenia (and thrombocytopenia) of epidemic hemorrhagic fever (23) (dengue and chikungunya viruses), Kyasanur forest disease (24), and the fatal pancytopenia of occasional cases of infectious hepatitis in man (25, 26) and malignant panleukopenia of cats (27). Phagocytosis of leukocytes, lymphocytes, red blood cells and platelets has been observed at autopsy in bone marrow specimens of cases of dengue and Japanese encephalitis (28).

LE Cells and Pseudo-LE Cells as Virus-Conditioned Phenomena: The observation that leukocytes incubated with a patient's serum may undergo lysis and phagocytosis by other leukocytes has had application in a variety of clinical conditions. The classic observation of this simple procedure is the LE cell phenomenon (29), particularly as induced by the method of Moffat, Barnes and Weiss in which normal blood leukocytes are incubated with LE serum (30). Heller and Zimmerman (20) described pseudo-LE cells as well as tart cells in tests in which leukocytes were incubated with serum of patients suffering from several diseases with postulated immunological basis, including rheumatoid arthritis, periarteritis nodosa, the nephrotic syndrome, glomerulonephritis, and various types of drug and foreign protein hypersensitivity.

Our own observations indicate that these effects can be duplicated when normal leukocytes are incubated with the virus-like agents that we isolated from the blood of SLE patients. In the case of vigorous strains isolated in acute and subacute SLE the changes in leukocytes were often morphologically indistinguishable from the LE cell phenomenon. In the case of the weaker agent isolated in chronic lupus erythematosus, the changes in leukocytes were nonspecific, being characteristic of "pseudo-LE cells", which differ from typical LE cells in the partial rather than complete homogenization of the inclusion body and also in the denser color of its periphery. In both instances tart cells were also present in abundance. These occurred also in controls, although in much smaller number.

Relationship of Autoantibodies to LE Cells: The observations described in this paper and in our previous papers favor the proposition that the LE factor of active LE serum is the representation of circulating blood-borne virus incorporated possible in the gamma globulin complex of the patient's serum and capable of acting either directly upon the substrate cells or in the form of immune complexes combined with complement. Such a proposition, if validated, may require reappraisal of the role of autoantibodies in the production of the LE cell. Similar considerations apply to the pseudo-LE cell even though the latter does not qualify as specific for lupus erythematosus.

The prevailing view of the LE cell factor as an autoantibody specific against nucleoprotein has been based largely on the observations that it is contained in the gamma globulin fraction of LE serum and, by inference, an immunoglobulin (31). This view is not altogether exempt from challenge. Despite the abundance of antibodies against nucleoprotein fractions in SLE, experimental attempts to reproduce the LE cell phenomenon with a variety of antigens including nuclear material have been generally unsuccessful (32). Among autoantibodies demonstrable in SLE are antibodies not only against components of nucleoprotein but also against cytoplasmic components such as mitochondria and microsomes, saline extracts of kidney, liver, and thymus tissues, platelets, clotting factors, Wassermann antigen and erythrocytes (33–36). What is also relevant is the observation mentioned in 1950 by Haserick and Lewis (37) that the LE factor could be separated from anti-LE serum by precipitating its gamma globulin with serum produced in rabbits against normal human gamma globulins the LE factor being retained in the supernate. It is difficult to imagine that the LE factor, if indeed a gamma globulin, would not have been precipitated with other gamma globulins. On the other hand a soluble immune complex composed of LE "virus" and homologous antibody would be located of necessity within the gamma globulin component of LE serum and, depending on the binding capacity of its antibody, would be dissociable with ease or difficulty by an antiglobulin antibody. A soluble immune complex of this composition would be as capable of coating leukocytes and encompassing their lysis as in the case of other types of immune complex, e.g., ovalbumin combined with homologous antibody (Waksman (38), and thus underlie the formation of the LE body (hematoxylin body). Stastny and Ziff (39) have suggested this possibility to account for lysis of lymphocytes in active SLE when exposed to rabbit complement. The same principle conceivably underlies the affinity of the LE factor for cell nuclei and various products of nuclear breakdown.

Parallels with "Autoimmune Disease" of NZB Mice: An extended discussion of the significance of autoimmune phenomena in SLE is beyond the scope of this paper. What may be germane are the striking parallels between SLE in man and the lupus-like viral disorder of NZB mice (40, 41). Multiplication of the virus in these mice is associated with eventual appearance in the blood of a factor capable of producing cells indistinguishable from LE cells. Other effects of the virus infection include the formation of antinuclear antibody, autoimmune hemolytic anemia, and immune complex diseases resembling the "lupus nephropathy" and "lupoid hepatitis" of human patients.

It would seem appropriate, as suggested by Fudenberg (42) and others (12, 43) that systemic LE in man, the disease of NZB mice, and other "autoimmune" diseases should all be regarded as antigen-antibody complex disease with viral antigens as the antigen.

With the model of virus-induced hemolytic anemia in mind, we advanced a similar concept in 1952, when we suggested that in certain cases of infection with a hemotoxic virus, e.g., Newcastle disease virus, the virus itself, or a noninfective viral residue or hemagglutinating component, may play the part of go-between, linking antiviral immune bodies to red cells (13). In the same paper we proposed that a similar intermediary role of virus receptors might be considered in the interpretation of certain other clinical phenomena in which the concept of "autosensitization" has been advanced, including disseminated lupus erythematosus.

Summary

Results of earlier studies in severe cases and the present studies in milder cases support the proposition that lupus erythematosus is associated consistently with a distinctive type of blood-borne virus-like agent transmissible in chick embryos. The agent was shown capable of inducing characteristic cytopathic changes in normal human leukocytes in vitro consisting of a spectrum ranging from tart cells and pseudo-LE cells to typical LE cells. The affinity of the agent for red blood cells was demonstrated in the form of virus-type hemagglutination and in the sensitization of the red blood cells of lupus patients in vivo to the agglutinating action of the homologous antiserum. These observations suggest that the interactions of this agent with blood cells underlie its dissemination within the body, the LE cell phenomenon in vitro, and some of the hematological complications of the disease.

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Chalones: A Mini-Review

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Introduction

Chalones are tissue-specific, species-nonspecific mitotic inhibitors. They have been found in every tissue examined for their presence including epidermis, lung, liver, melanocyte, kidney, granulocyte, lymphocyte, testes, erythrocyte, fibroblast, lens, uterus, intestine, muscle, stomach, and cheek pouch (1–16). The word chalone, from the Greek *chalao,* to "lessen or lower," was first proposed by Schafer in 1906 as a theoretical counterpart to "hormone." The chalone concept was paid little heed until 1960 when Bullough and Laurence began to assemble the first experimental evidence for the presence of chalone. For the first time, inhibition as opposed to stimulation was invoked in attempting to explain the phenomenon of tissue regeneration and its control.

Chalone was the subject of intensive research throughout the sixties. Biochemical studies revealed that chalones were proteins of two distinct molecular weight classes (2,000–6,000 daltons and 20,000–50,000 daltons). While basic researchers focused on specific interaction in the cell cycle, clinicians became interested in the potential application of chalone treatment of diseased states characterized by rampant mitotic activity. We will briefly outline the major concepts of chalone mechanisms, current applications and future possibilities in order to stimulate interest in this important field (17).

Chalone Mechanisms

The regulation of cell growth has been the subject of experimental and theoretical work throughout the era of modern biology. The major controversies have centered around two points: 1) whether control is stimulatory or inhibitory and 2) whether the site of control is central or self-contained in each tissue type. Early theories favored a stimulatory mechanism. For example, in 1892 Wiesner attributed increased mitotic activity following a wound to a stimulatory substance secreted by the injured cells. Central control theories have also been proposed such as Tanner's notion that the brain, preceding all other tissues in ontological development, mediates cell growth (18). The chalone represents a departure from earlier cellular control concepts by demonstrating in situ production of inhibitory substances.

Evidence supporting inhibitory control began to accumulate in the early 1950's. Rose, in 1952, showed embryonic tissue inhibition following addition of adult extracts of the same tissue type (19). In the same year, Glinos and Gey found that mere dilution of plasma resulted in mitotic stimulation of hepatic cells (20). Furthermore, it was demonstrated that serum from a normal rat

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inhibits regeneration while serum from a partially hepatectomized rat causes increased regenerative activity in the liver (21). These results indicate the presence of a freely diffusible substance inhibitory to cell proliferation.

Work in the 1960's by Iverson, Bullough, and Laurence provided the first comprehensive study of cell growth inhibitors as well as enhancing further research in the field. Iverson's proposed model for epidermal growth control includes a system in which differentiated cells continuously produce an inhibitory substance. A concentration gradient is established from high levels in the epidermal surface to low levels in the basal layer (22). Thus, this theory can account for a steady production of non-dividing keratinized cells.

Bullough and Laurence, in a series of classic experiments, studied the mitotic activity following epidermal injury (1). Excision of a small portion of epidermal tissue from the mouse ear resulted in increased mitotic activity of epidermal tissue on the opposite side of the ear. This response was confined to within 1 mm of the wound edge. It was theorized that removal of ear tissue resulted in decreased presence of a locally produced inhibitor. This was, in fact, confirmed by Bullough when he isolated a tissue specific mitotic inhibitor from porcine epidermis (23). The protein fraction isolated (2,000–3,000 daltons) was termed chalone. Further support for Bullough's discovery came from the work of Feingold demonstrating that replacement of excised tissue suppressed proliferation opposite the wound (24).

A major problem, however, remained. Although Bullough hypothesized that chalones act at the G1-S boundary, serving as switch between cell division and maturation, a mitotic block could only be observed at the G2 phase. The dilemma was resolved when Marks succeeded in isolating an additional epidermal chalone specific for interacting at the G1 phase (25). The G1 inhibitor appears to be the controlling factor envisioned by Bullough while the role of the G2 chalone remains to be elucidated. It has been speculated that some epidermal cells are maintained in the G2 phase (5–10%) in order to affect a rapid production of new cells in the event of injury. This functional dichotomy is, in part, supported by the observation that G1 chalones are found mainly in the superficial layer while G2 chalones are principally found in the basal layer (26, 27).

Epidermal chalone studies stimulated investigation of chalone systems in many other tissues. Increased acceptance has led to the proposal of numerous mechanisms by which chalones may act. Although discussion of all proposed mechanisms is not feasible, some of the major theories will be outlined.

Intracellular levels of cyclic AMP (cAMP) appear to correlate with mitotic activity. In actively dividing and growing cells low concentration of cAMP has been observed, while addition of dibutyryl cAMP restored controlled cell growth (16). Attallah proposed that chalones may contain two active sites, one specific for the cell membrane and the other site non-specific for stimulating adenyl cyclase (28). Chalones, therefore, may be responsible for maintaining high levels of cAMP which, in turn, inhibits nucleoside kinase activity necessary for DNA synthesis.

Experimental evidence from the work of Attallah and Houck on lymphocyte

chalone supports the connection between chalone and cAMP (29). Examining chalone activity in a PHA (phytohemagglutinin) stimulated culture led to the following findings: 1) chalone inhibition decreased as the time interval between PHA and chalone increased, 2) both chalone and cAMP exert their effect on thymidine incorporation prior to nucleoside entry in the DNA precursor pool and 3) inhibition was dependent solely on the concentration of chalone added. The latter finding suggests that once chalone-induced changes have occurred the cell will not respond to further addition of cAMP.

That the site of chalone action is on the cell membrane is further supported by the observation of contact inhibition in normal cell cultures. Though presumably chalone is present in the membrane of an individual cell it does not result in mitotic inhibition until additional cells are in surface contact with each other. This concept forms the basis of what has been termed the "chalone bridge model" (30).

An alternate mechanism proposes a more indirect connection between chalones and cAMP. Gelfant et al observed that mitotic activity is decreased by translational inhibitors and increased by actinomycin D (31). Since actinomycin D is known to inhibit translational repressors, it was proposed that the G2 chalone may act as a posttranscriptional repressor of messenger RNA coding for a protein product essential for mitosis. The high intracellular concentrations of cAMP may be necessary to activate chalone via phosphorylation.

We have gone into some detail on the relationship between chalone and cAMP to serve as an example of present research into chalone mechanisms. It should be made clear that the actual mechanism is probably an exceedingly complex interaction of many different substances. Adrenalin and glucocorticoids, for example, appear to be involved (32, 33). A complete delineation of a chalone mechanism must await further advances in chalone biochemistry.

Potential for Clinical Use

It is evident that ramifications of chalone studies are enormous. A diseased state characterized by uncontrolled mitotic activity may be the result of a deficient chalone mechanism. Injection of the proper tissue specific protein may lead to restoration of the normal state.

The most obvious diseased state characterized by rampant cell growth is cancer. Indicative of all growing tumors is a rate of cell production greater than cell loss. The possibility that increased mitotic activity may be due to a chalone anomaly dominated early chalone-cancer work. Bullough and Laurence (34) and Rytomaa and Kiviniemi (35) first studied the chalone mechanism in rabbit epidermal carcinoma and rat granulocytic leukemia, respectively. In both cases, the intracellular chalone concentration was 1/10 or less the concentration found in normal tissues. Injection of exogenous chalone restored mitotic inhibition. These early observations have been supported by studies in other tumors such as Chernoremski hamster epidermal carcinoma (36), Harding-Passey mouse melanoma (4), lymphoblastic leukemia (37) and spontaneous granulocytic leukemia (38).

Injection of appropriate chalones have been employed to stop and even reverse tumor growth. Rytomaa and Kiviniemi used granulocyte chalone in attempts to destroy Shay granulocytic leukemia (of the granuloma and dispersed leukemic forms) in the rat (35). Following three to six weeks of repeated chalone injection, granulomatas were destroyed, and in many cases, permanently. Results with dispersed leukemia were even more dramatic. In 40 animals tested, repeated injection of bovine granulocyte chalone over three to four weeks resulted in complete cure in nine animals.

In a clinical test of seven human patients with myeloid leukemia, Rytomaa and Kiviniemi reported granulocyte chalone treatment resulted in leukemic regression in five cases. In one case, a complete remission was observed. Interestingly enough, additional effects of chalone treatment included immunostimulation and increased resistance to bacterial infection (39).

It has been suggested that chalone treatment may be useful in conjunction with present day chemotherapeutic agents (40). For example, the lymphocyte chalone is known to arrest normal and tumor cells in the G1 phase and has been found to be cytotoxic to leukemic lymphocytes in the dormant (G1-G0) state. The cytotoxicity, therefore, would kill large numbers of cells in this phase. The reduction of lymphocyte chalone in vivo would release leukemic cells from G1 inhibition and allow them to proceed synchronously to the S phase. At this point, chemotheraputic agents specific for S phase cells could be used to destroy the leukemic cells. It is important to note that reduction of the chalone dose would not be sufficient to release normal cells from G1 inhibition.

The ability of the lymphocyte chalone to inhibit cell proliferation in vitro has led to the investigation of its possible use as an immunosuppressive agent for organ transplantation. Houck attempted skin graft prolongation in C57BL/6 mice receiving skin allotransplants from C3H mice (41). Control mice rejected skin grafts in 12 days while animals injected with lymphocyte chalone maintained skin grafts for 29 days, approximately eight to ten days after the final chalone injection. Unfortunately, the large amounts of chalone needed for in vivo work makes experimentation in any animal larger than the mouse extremely costly and practically impossible.

Chalone treatment of other diseased states may be possible. Initial studies with a putative smooth muscle cell (SMC) chalone have been promising. Treatment of arteriosclerotic plaques with SMC chalone may some day be a reality (42).

Conclusion

The chalone concept is provocative in both its scope and implications. Complete elucidation and confirmation of a chalone system could result in major advances in the biology of cell regulation and in the successful treatment of several diseases. There is a need, then, to check the natural enthusiasm that arises upon an initial exposure to chalones by taking a critical look at the current state of knowledge. There are, in fact, several formidable problems.

Houck and Hunt have recently summarized the primary technical problems that face the chalone researcher (43). Firstly, bacterial contamination has been

shown to mimic chalone action. Mohr et al found that Clostridium spores in their extract had the ability to inhibit cell proliferation in the epidermis, reversibly and with no cytotoxicity. Houck encountered a similar problem with lymphocyte chalone extract in which an unknown bacterial contaminant was shown to inhibit PHA stimulation in a lymphocyte cell culture.

Secondly, the use of tritiated thymidine incorporation as an index of mitotic activity can result in many experimental artifacts. The presence, in tissue extracts, of either concentrated levels of enzymes which degrade thymidine or large amounts of unlabelled thymidine can cause spurious results.

Thirdly, a cytotoxic effect of tissue extracts is possible. While presumably normal tissue does not contain cytotoxic substances, the concentration procedure may result in abnormally high levels of compounds with a harmful effect on cell viability (e.g., membrane degrading enzymes).

These problems, of course, could be totally overcome by the complete isolation and purification of chalone. Unfortunately, efforts in this direction have been frustrating; the problem requires a considerable degree of biochemical sophistication. The major complicating factors are the very low concentration in which chalone probably exists, apparent RNA complexing with chalone (46), and strong aggregation of different proteins (47). The complete acceptance of the chalone hypothesis must await the isolation of a purified, fully characterized chalone.

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Talcosis and Coronary Artery Disease

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Abstract

Arteriosclerotic heart disease and talcosis coexisted in 45 male patients who had had an industrial exposure to talc. The patients demonstrated a high incidence of hypertension, 29 of 45, obesity 35 of 45, and of hypercholesteremia, 28 of 41. They were almost all cigarette smokers, 39 of 44, and usually had a positive family history of cardiovascular disease. No individual was completely free of risk factors. Talcosis patients often have arteriosclerotic heart disease which has not previously been documented.

Introduction

Talc pneumoconiosis or talcosis was first described in 1896 by Thorel (1). Since then there have been numerous reports on the clinical, physiological, and pathological manifestations of talcosis. Most previous reports have dealt exclusively with the pulmonary disability (2, 3, 4). Cardiovascular disease often complicates talcosis, but concurrence has been poorly documented. This report deals with the arteriosclerotic cardiovascular disease which often accompanies talcosis. We specifically excluded cor pulmonale.

One paper published in 1963 reported on six autopsied cases (5). Two of the cases fail to mention the heart with a history of severe chest pain! One of the two was a 49-year-old male. In three of the remaining four cases, coronary atherosclerosis was mentioned. A separate study identified heart disease (other than cor pulmonale) as cause of death in 27.5%, ninety-one talc workers (6).

In a more recent paper the proportional mortality from cardiac disease was observed to be lower (7). The authors did not present data on clinically significant coronary artery disease, but only on mortality. There has been no published study dealing with the concurrence of symptomatic arteriosclerotic heart disease and talcosis. We report our experiences with a group of talc workers who were seen because of symptomatic coronary artery disease.

Materials and Methods

We studied 45 men that had talcosis as well as arteriosclerotic heart disease. Each patient had been exposed to talc dust for at least twelve years. Each patient received a complete history, physical examination, chest x-ray, electrocardiogram, pulmonary function study, including vital capacity and maximum breathing capacity, complete blood count, urinalysis, total blood sugar, uric acid, cholesterol, and triglyceride. The blood tests were taken on fasting patients. The risk factors—obesity, hypertension, hyperlipidemia, smoking, and family history of vascular disease—were evaluated. Where possible, rec-

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ords of examinations by other physicians and previous hospital records were obtained and analyzed.

Hypertension was defined as blood pressure greater than 140/90. Cholesterol greater than 240 mg % was considered elevated. Individuals who were 15% over ideal weight were considered obese. Arteriosclerotic heart disease was diagnosed by a history of typical angina pectoris, or by electrocardiographic evidence of myocardial infarction. In each case where definite myocardial infarction could not be documented, the patients gave a history of exertional precordial pain which was relieved by rest and/or nitroglycerine. A history of precordial pain on exposure to cold and after eating a heavy meal was often obtained. In a few instances the patients have shown an abnormal response to exercise stress tests. They had been followed for their talcosis and heart disease by their personal physicians for several years prior to referral for cardiac evaluation.

Results

The 45 while male talc miners ranged in age from 40 to 68 years (mean 55). They had been exposed to industrial talc for 12 to 46 years (mean 26). Hypertension was present in 29 of the 45 men (64%), and 35 were obese (78%). Cholesterol values exceeded 240 mg % in 28 of 41 subjects (68%), the mean cholesterol for the entire sample was 261 mg %. Triglyceride determinations were available in 39 miners, 15 exceeded 150 mg %. The mean triglyceride of all 39 was 162 mg %. A family history of cardiovascular disease or stroke was found in 33 of 41 men. A history of smoking was documented in 44 and there were 39 smokers (89%). The average smoker had accumulated 38 pack years. Electrocardiographic abnormalities were documented in 36 of 44 cases. Seven had definite myocardial infarctions and 29 had non-specific ST/T abnormalities.

The complete results of this study are listed in Tables I and II.

We then examined each individual for the concurrence of risk factors. The six risk factors studied were obesity, hypertension, elevated cholesterol, triglyceride over 150 mg %, history of smoking, and presence of a positive family history for vascular disease. See Table III.

Note that most had 3 or more risk factors, and none had no risk factors. Only 2 had a single risk factor. The average patient had 3.8 risk factors. Data on the vital capacity and maximum breathing capacity was available on 44 of the patients and was always diminished. Resting PO2 determinations were available in 27 instances and was diminished in 24. Chest x-rays were available in 44 instances and were normal in only 1. The lung fields showed varying degrees of fibrosis and there were occasional pleural changes. Cardiomegaly was present in 15 patients. Uric acid determinations were available for 35 patients, the level exceeded 6 mg % in 19.

Discussion

The frequency of occurrence of coronary atherosclerotic disease in talcosis does not imply an etiologic relationship. The development of vascular disease

TABLE I

Pulmonary Disease Factors

Name	Age	Years exposed to talc	Vital cap.	L. Max. B.C. L/M	PO2	X-Ray*	(Packs Smoked years)
DH	54	33	3.6	78	64	2	53
EB	59	37	3.0	100	68	WNL	0
RC	60		30.0		2	Many	
			90				
CG	65	18	2.8			2	78
TM	55	28	2.0	55		2	15
JH	66	46	2.2	64		2	41
HS	52	28	2.5	106	95	2	20
MR	52	25	1.4	less than 30	82	2	20
MS	49	29	3.5	95	66	2	20
ES	52	28	2.6	88		1 + 2	0
FL	51	20	2.7	60	69	1 + 2 + 3	15
JP	48	30	2.9	35	80	1 + 2	20
WM	68	36	2.5	96	86	1 + 3	0
RM	40	16	3.0	120		1 + 2 + 3	27
EM	42	20	3.4	75		2	10
WM	57	28	1.5	36		1 + 3	45
AM	68	46	2.4	69		2	50
HW	64	26	3.0	80		1 + 2	60
WG	62	33	3.2	100		2	10
CK	55	27	1.9	46		2	
WS	60	20			74	2	
OG	65		less than 1.0	less than 30			30
MG	45	23	3.0	64		2	10
RH	56		1.8	36	78	1 + 3	30
RM	58	27	2.4	54	67	1 + 2	70
EF	55	34	3.0	90	80	1 + 2	26
GP	64	37	2.6	69	82	3	
LM	47	21	1.3	40	92	2	28
GM	41	15	1.7	65		2 + 3	20
CC	58	18	2.2	53	80	2 + 3	47
WP	48	18	2.5	100	83	2	41
TB	63	24	2.5	47	76	2	44
MJ	55		2.4	less than 30	75	2	60
SA	49	28	2.2	104	61	1 + 2	30
HW	60	23	2.5	71	69	1 + 2	40
AS	66	45	2.5	126	91	2	0
GW	60	30	2.6	90	85	2	53
VB	64	22	3.2	50		3	30
JN	55	21	2.5	60	61	1 + 3	18
DB	56	22	2.5	75		1 + 2	35
CN	63	12	2.5	80	75	2	60
CG	50	18	2.5	68	65	1 + 3	0
OC	55	25	2.7	92	79	2	60
WM	52	22	3.5	120		2	45
PH	55	24	1.0	48	93	2	113

* X-ray findings:

1 = Cardiomegaly
2 = Increased fibrotic markings
3 = Abnormal densities

TABLE II

Risks of Cardiac Disease

Name	Age	Ht.	Wt.	B/P	Chol.	M6% Trig.	M9% Fam. His.	U.A.	M6% EKG.*	Smoke (Pack years)
DH	54	5′9″	213	150/100	225	154	Pos.	5.7	WNL	53
EB	59	5′5″	207	150/100	320	140	Pos.	5.6	1	0
RC	60	6′1″	175	140/70	248	70	Pos.	6.4	1 + 2	Many
CG	65	5′4″	157	165/105	180		Neg.	6.1	WNL	78
TM	55	5′6″	161	160/90			Pos.		2	15
JH	66	5′8″	220	160/100	199	135	Neg.	7.5	WNL	41
HS	52	6′	146	120/80	172	110	Pos.	3.2	1	20
MR	52	5′9″	177	220/120	328	105	Neg.	7.5	2	20
MS	49	6′	198	160/90	254	95	Pos.	5.0	1	20
ES	52	5′11″	235	140/100	250			7.2	1	0
FL	51	5′9″	222	130/80	244	420	Pos.	8.1	WNL	15
JP	48	6′1″	273	160/100	275	116	Pos.	6.5	WNL	20
WM	68	5′11″	177	140/90	230	68	Pos.	3.1	2	0
RM	40	5′10″	219	160/90	334	210	Pos.	12.5	1	27
EM	42	5′7″	152	132/88	229	74	Pos.	4.6	WNL	10
WM	57	5′10″	203	160/110	292	271	Neg.	6.2	1	45
AM	68	5′8″	165	130/80	212	92	Neg.	5.5	WNL	50
HW	64	5′10″	227	140/90	276	286		6.7	1	60
WG	62	6′	151	120/80			Pos.		1 + 3	10
CK	55	5′10″	184	124/84	306	125	Pos.	8.4	2 + 4	
WS	60	5′6″	147	197/125			Pos.		1	
DG	65	5′2″	160	160/90	240	174	Pos.		2	30
MG	45	5′10″	195	160/100	236	198	Neg.	7.2	WNL	10
RH	56	5′8″	181	140/100	290	63	Pos.	5.0	1	30
RM	58	5′7″	161	152/92	204	40	Pos.	8.9	1	70
EF	55	5′11″	256	170/120	275	690	Neg.		1 + 4	26
GP	64	5′8″	189	150/110	279	210	Pos.	7.3	1	
LM	47	5′10″	166	130/90	263	68	Pos.		4	28
GM	41	5′10″	198	140/100	312	230	Pos.	7.7	1	20
CC	58	5′9″	202	140/90	206	212	Pos.		1	47
WP	48	5′10″	165	160/104	305	122	Pos.	4.1	1	41
TB	63	5′8″	201	140/100	226	146	Pos.		1	44
MJ	55	5′4″	151	140/80	285	50	Pos.	8.2	1	60
SA	49	5′11″	209	120/80	291	162	Pos.	5.8		30
HW	60	5′8″	194	160/90 .	248	104		5.2	1	40
AS	66	5′6″	178	140/80	380	309	Pos.	6.5	2	0
GW	60	5′8″	172	142/102	200	66	Pos.	4.1	1	53
VB	64	5′8″	220	110/78	277	67		5.7	1	30
JN	55	5′7″	172	164/104	312	88	Pos.	6.1	1	18
DB	56	5′10″	216	160/108	275	117	Pos.	4.6	1	35
CN	63	5′8″	160	180/100	260	113	Pos.	4.6	1	60
CG	50	6′1″	197	150/110			Neg.		1	0
OC	55	5′6″	165	130/88	243	69	Pos.	5.7	1	60
WM	52	6′	210	140/100	328	232	Pos.	7.0	1	45
PH	55	6′	260	150/100	272	300	Pos.		1	113

* EKG findings:

1 = ST/T abnormalities
2 = Myocardial infarction
3 = Left ventricular hypertrophy
4 = Chronic pulmonary disease

TABLE III

Number of risk factors present	Number of individuals
6	4
5	11
4	12
3	10
2	6
1	2
0	0

has been shown to relate to a variety of so called risk factors which have been previously documented (8). In all likelihood it is the frequency of smoking, and excessive intake of calories, cholesterol and saturated fats which result in the high incidence of coronary atherosclerosis.

The concurrence of talcosis and symptomatic coronary artery disease appears to be frequent. The patients studied had a high incidence of risk factors. Surprisingly, little information on the presence of coronary artery disease is available from previously autopsied cases. Indeed, most published autopsies on talcosis victims fail to describe any dissection of the coronary arteries (9).

The relationship of talcosis to the atherosclerotic process is unknown. There may be no direct connection. The effect of severe pulmonary disease on coronary artery disease is more comprehensible. The pulmonary fibrosis associated with talcosis has been shown to reduce vital capacity, maximum breathing capacity, and ultimately PO2 (10, 11, 12). The patients studied had reduced vital capacity, maximum breathing capacity, and PO2. The resultant hypoxia tends to aggravate preexisting angina pectoris by making the patient symptomatic at lesser degrees of physical stress. In those patients in whom PO2 studies at rest were available, they were significantly diminished. With exercise the PO2 would have been even lower. The resulting anoxia can aggravate pre-existing coronary artery disease. The heart extracts most of the available oxygen from coronary blood flow. Any reduction in the oxygen content may be critically related to symptoms of ischemia. In a previously compromised coronary circulation, even marginal reduction in available arterial blood oxygen may result in symptomatic aggravation.

Victims of talcosis often have combined pulmonary and anginal disability. The presence of heart disease should be more vigorously investigated in future cases of symptomatic talcosis.

Summary

A group of 45 white males with talcosis and arteriosclerotic heart disease were studied. They ranged in age from 40 to 68 years. Obesity was present in 35/45 or 78%, hypertension was present in 29/45 or 64%. Cholesterol exceeded 240 mg % in 28/41, and triglyceride values in 15/39 exceeded 150 mg %. Thirty-three of forty-one had a positive family history and 39/44 or 89% were smokers. The high incidence of cardiac risk factors among these men may explain the high incidence of cardiovascular disease. The relationship between their pul-

monary and cardiac disease is discussed. Patients with symptomatic talcosis should be investigated for the presence of complicating coronary artery disease.

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Nonrheumatoid Pleural Effusions in Patients with Rheumatoid Arthritis

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Abstract

The clinical and pleural fluid findings in six patients with rheumatoid arthritis and nonrheumatoid pleural effusions are described. Nonrheumatoid origin of pleural effusion is suggested by female sex, inactive joint disease, absence of subcutaneous nodules, presence of a cause for pleural effusion such as congestive heart failure, pneumonia, or carcinoma, and negative or low serum latex fixation titers. Confirmatory pleural fluid findings are absence of rheumatoid arthritis (RA) cells, concentrations of protein below 3 gm/100 ml, sugar above 50 mg/100 ml, lactic dehydrogenase below 350 mU/ml, and cholesterol below 300 mg/100 ml.

Introduction

Pleural effusion is a well recognized extra-articular manifestation of rheumatoid arthritis (1–3). Low sugar levels (2, 4), high lactic dehydrogenase (LDH) (5), positive latex fixation test (5), presence of rheumatoid arthritis (RA) cells (5), elevated cholesterol and lipids (2), diminished complement (6), and a unique cytologic appearance (7) have been described in pleural fluid in rheumatoid pleurisy.

There is little information in the literature describing pleural fluid findings in patients with rheumatoid arthritis whose effusions are not rheumatoid in origin.

We report six rheumatoid arthritis patients with pleural effusions due to congestive heart failure, pneumonia, and metastatic carcinoma, and contrast the clinical features and pleural fluid findings with those seen in rheumatoid pleurisy.

Methods

Six patients with definite rheumatoid arthritis and pleural effusions due to congestive heart failure, pneumonia, and metastatic carcinoma were studied at the Mount Sinai Services–City Hospital Center at Elmhurst between July 1964 and February 1976. The diagnosis of rheumatoid arthritis was established by the usual history, physical findings, and radiographic studies.

In four patients with known arteriosclerotic heart disease and congestive heart failure, pleural effusion diminished when diuretics, digitalis, and low salt diet were administered. Productive cough, fever, lower lobe infiltrations on chest roentgenogram, and response to antibiotics were noted in the patient with pneumonia. The patient with neoplastic effusion had a previous abdom-

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inal exploration showing ovarian carcinoma and a current pleural biopsy demonstrating malignant changes. Pleural biopsies with the Abrams needle were performed in five patients.

Results

The age, sex, activity and duration of rheumatoid arthritis, occurrence of subcutaneous nodules, serum latex fixation test, and clinical diagnoses of the six patients studied are included in Table I. Fluid obtained by thoracentesis was clear yellow except in the patient with carcinoma in whom bloody fluid was found. Pleural biopsies showed acute and chronic nonspecific inflammation in four patients and carcinoma in one patient. None of the pathologic findings resembled those of a rheumatoid nodule.

Table II summarizes differential leukocyte counts, presence or absence of RA cells, and determinations of pleural fluid protein, sugar, lactic dehydrogenase, latex fixation test, complement, and cholesterol.

Discussion

Clinical and pleural fluid findings distinguish these six patients with nonrheumatoid pleural effusions from patients with rheumatoid pleurisy. Although rheumatoid arthritis is more common in women, rheumatoid pleurisy occurs predominantly in men (1, 2). Patients with pleural effusion due to rheumatoid disease have active rheumatoid arthritis, often with exacerbations of joint disease at the onset of pleurisy, and usually have subcutaneous nodules (1, 4).

TABLE I

Clinical Features and Diagnoses in 6 Patients with Nonrheumatoid Pleural Effusions

	Age	Sex	Activity and Duration of Rheumatoid Arthritis	Subcutaneous Nodules	Serum Latex Fixation Test	Clinical Diagnosis
1	60	M	inactive—4 years	present	negative	ASHD, CHF
2	70	F	active—4 weeks	absent	positive	ASHD, CHF
3	53	F	inactive—5 years	absent	negative	Pneumonia
4	55	F	inactive—4 years	absent	negative	Metastatic carcinoma
5	72	F	inactive—20 years	absent	negative	ASHD, CHF
6	69	F	inactive—10 years	absent	negative	ASHD, CHF

TABLE II

Pleural Fluid Findings in 6 Patients with Nonrheumatoid Pleural Effusions

	Differential Leukocyte Count % Lymphocytes	RA Cells	Protein gm/100 ml	Sugar mg/100 ml	LDH mU/ml	Latex Fixation Test	Complement mg/100 ml	Cholesterol mg/100 ml
1	71	—	2.2	126	100	negative	40	—
2	100	not seen	2.9	110	130	positive	40	—
3	100	—	5.5	80	350	negative	(serum 230)	152
4	40	—	5.2	8	3000	negative	—	72
5	93	not seen	2.3	148	180	negative	—	—
6	83	not seen	3.8	160	140		45	70

Our series includes only one man, one patient with active arthritis, and one with subcutaneous nodules. The occurrence of pleural effusion in a patient with congestive heart failure, pneumonia, or malignancy, particularly in a woman with inactive joint disease and without subcutaneous nodules, suggests that the effusion is not due to rheumatoid disease.

High serum latex fixation titers are usually found in rheumatoid pleurisy (1). Only one patient had a positive serum latex fixation test.

Pleural biopsy and studies of pleural fluid may help confirm a diagnosis of rheumatoid pleurisy. Occasionally pleural biopsy abnormalities resemble those seen in rheumatoid nodules (1, 5). None of our patients demonstrated these changes, but pleural biopsy established the diagnosis of malignancy in one patient.

Differential pleural fluid cell counts are not useful in diagnosis of rheumatoid pleurisy (1). Lymphocytosis is most common (1). Occasionally pleural eosinophilia is seen (3). In our patients total and differential leukocyte counts resembled those usually found in the underlying condition, e.g., heart failure, pneumonia, or carcinoma. We did not detect the unique cytologic picture described in rheumatoid effusions—a background of orange or red granular material, large elongated cells, and giant round or oval multinucleated cells (7). Rheumatoid arthritis (RA) cells similar to those occurring in rheumatoid joint effusions have been identified in rheumatoid pleural fluid, but were not found in three of our patients (5).

Pleural fluid protein is usually greater than 3 gm/100 ml in rheumatoid effusions (1). Lower values suggest that the fluid may be due to congestive heart failure as seen in three patients.

Carr and Mayne (4) reported pleural fluid glucose levels below 30 mg/100 ml in 10 of 11 fluids tested in patients with rheumatoid arthritis. Lillington et al (2) stated that pleural glucose was below 30 mg/100 ml in 70 to 80% of patients but that another disease process may have caused the pleural effusion in some, including three of their own patients. Pleural fluid glucose concentrations of 8 mg/100 ml, as found in the patient with metastatic carcinoma, have been reported in malignant pleural effusions (8).

Extremely elevated pleural fluid lactic dehydrogenase levels have been described in rheumatoid pleurisy (5). Only the patient with malignant effusion had high values. Elevated lactic dehydrogenase levels occur commonly in malignant effusions.

Positive pleural latex fixation tests have been reported in rheumatoid pleural effusions (5) but have also been seen in 14 to 41% of patients with tuberculosis, carcinoma, and pneumonia (9). Only the patient with active rheumatoid arthritis and congestive heart failure had a positive test.

Pleural fluid complement levels may be diminished in rheumatoid pleurisy (6). Three patients had low pleural complement values—40 to 45 mg/100 ml. Serum complement was 230 mg/100 ml in one of these patients. We do not know the significance of these findings but one patient from our hospital with rheumatoid pleurisy had a pleural complement of 26 mg/100 ml. Three pleural fluid cholesterol concentrations were not elevated. Some patients with rheumatoid effusion have increased pleural cholesterol or total lipids (3).

Absence of RA cells, pleural protein concentration below 3 gm/100 ml, sugar above 50 mg/100 ml, lactic dehydrogenase below 350 mU/ml, and cholesterol concentration below 300 mg/100 ml point to a nonrheumatoid origin of pleural effusion in patients with rheumatoid arthritis.

The data presented suggest that the pleural fluid changes described in rheumatoid pleurisy are specifically due to rheumatoid inflammation of the pleura since they are not found when pleural effusion is due to other causes in patients with rheumatoid arthritis.

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Abdominal Ultrasonography and Computerized Tomography—Anatomic Correlation Illustrated by Findings in Ascites

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Abstract

Anatomic features demonstrated by abdominal gray scale ultrasonography and computerized tomography can be correlated, detail for detail, despite basic differences in method of detection. This is well demonstrated in patients with ascites. In a typical case, intraperitoneal fluid assists in separating and identifying the outlines of individual viscera and bowel loops. The distribution of bowel loops follows a pattern determined by the attachments of the mesentery, transverse and sigmoid mesocolon and peritoneal reflections. This pattern is seen in the majority of patients with considerable amount of ascitic fluid.

The respective roles of gray scale ultrasonography (B-scan) (1, 2) and computerized tomography (CT scan) in the detection and delineation of abdominal abnormalities are under intensive investigation. For this purpose, it is necessary to identify similar structures and to determine whether one or the other modality has an advantage. The presence of free fluid within the peritoneal cavity assists in the separation and delineation of individual viscera by both methods. The pattern which is seen in the majority of patients with ascites is illustrated by the following case—a prototype of the findings in more than 50 similar examples.

Case: The patient was a moderately obese 48-year-old female with ascites of several months duration. Several years prior to admission, a carcinoma of the breast had been resected. She was examined first by ultrasound (Rohnar system 5555) and, two hours later, by a computerized total body scanner (Delta 50 Scanner). Ultrasonography was done with a 2.25 MHz 13 mm transducer, displayed on a television monitor in gray scale and recorded on Polaroid film. Computerized scanning was done 30 minutes after ingestion of 300 ml of twenty times diluted gastrografin. No contrast medium was injected intravenously. The thickness of each section was 8 mm. The patient was supine during both examinations.

Anatomic Description

Figure 1 indicates diagrammatically the various planes of section illustrated in Figures 2 and 3. Correlation of specific features was facilitated by having both modalities available although the diagnosis was clear in both. No abdominal masses were demonstrated by either technique. In both examinations, a considerable amount of fluid was demonstrated anterior and lateral to the liver. With the patient supine, no fluid was seen posterior to the liver, i.e.,

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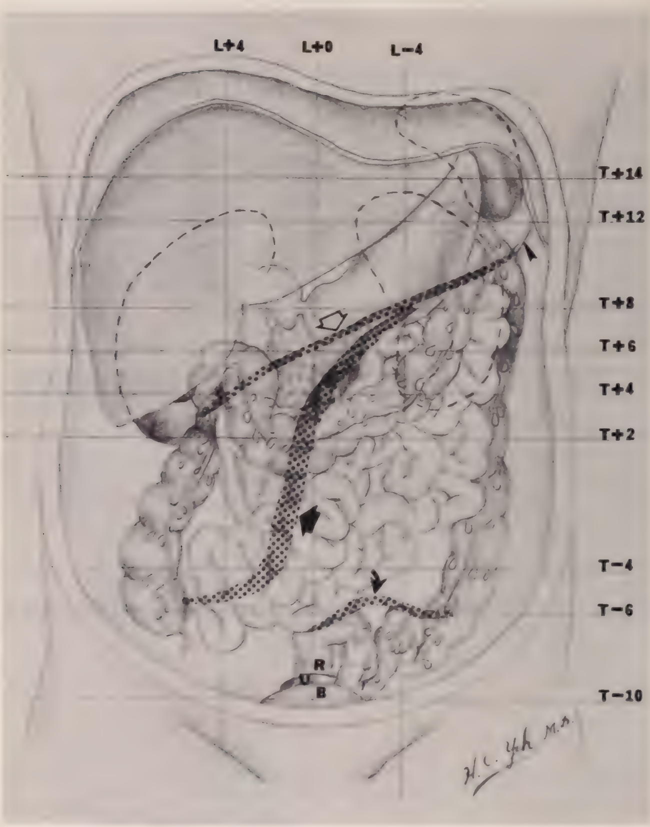

FIG. 1. Schematic drawing of the abdomen of the patient to indicate planes of section illustrated in figures 2 and 3. Transverse planes are designated by T with "+" specifying centimeters above umbilicus and "−" centimeters below umbilicus. Longitudinal scans are specified by L with "+" indicating planes to the right of the midline and "−" to the left. Dotted areas represent retroperitoneal mesenteric attachements; open arrow = root of transverse mesocolon; solid thick arrow = root of small bowel mesentery; curved arrow = sigmoid mesocolon root; arrowhead = phrenicocolic ligament. *Abbreviations:* R = rectum; U = uterus; B = bladder. "Empty" intraperitoneal spaces should be visualized as occupied by fluid.

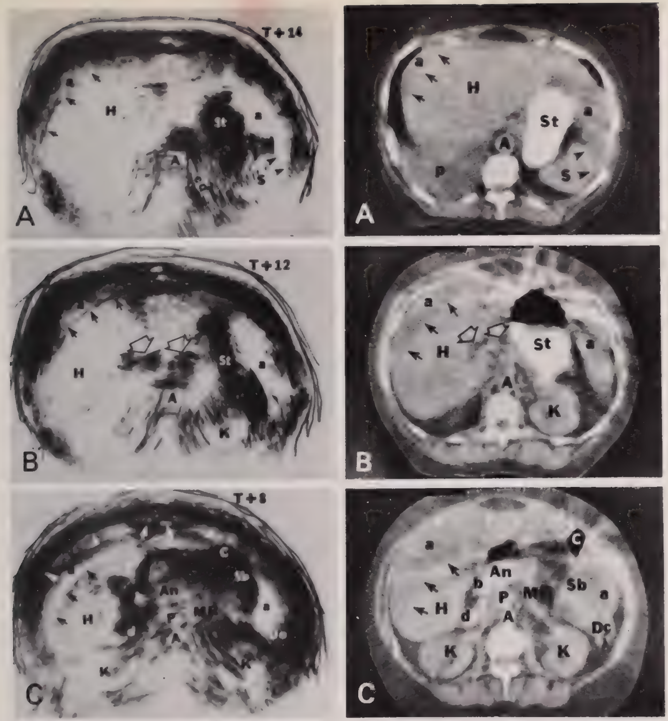

FIG. 2. Corresponding transverse B-scans and computerized tomograms; supine, right side of patient on reader's left. Unprimed figures are B-scans, primed figures, CT scans. *Abbreviations:* A = aorta; Ac = ascending colon; An = gastric antrum; a = ascitic fluid; B = bladder; b = duodenal bulb; C = transverse colon; cc = caput coli; cd = crus of diaphragm; Ch = hepatic flexure; d = duodenal loop; Dc = descending colon; H = liver; iw = iliac wing; K = kidney; MC = transverse mesocolon; MR = mesenteric root, smallbowel; P = pancreas; R = rectum; S = spleen; Sb = small bowel; Sc = sigmoid colon; St = stomach; U = uterus.

FIG. 2A, 2A′. 14 cm above the umbilicus (T+14). A small amount of ascitic fluid is present anterior and lateral to the liver. In the B-scan, this region is not echo-free due to reverberations. However, the lateral border of the liver (arrows) is separated from the rib cage. Ascitic fluid is also present lateral to the spleen (arrowheads) and to the stomach. In the CT scan, stomach contains contrast material.

FIG. 2B, 2B′. 12 cm above the umbilicus (T+12). The amound of fluid lateral to the liver is larger. The large open arrows indicate the region of the porta hepatis and lesser omentum—echogenic on the sonogram and lucent on the CT scan. Arrows indicate interface between ascitic fluid and liver.

FIG. 2C, 2C′. 8 cms above the umbilicus (T+8). White arrowheads indicate parietal peritoneum. More fluid is present lateral to the liver. Echo-free area deep to the reverberation echoes is now present since the thickness of fluid is greater. A small amount of gas in the distal transverse colon and in the gastric antrum is not evident in the B-scan. Perhaps air was not present at the time of the sonogram or was obscured by the compound scanning. The dilute opaque material in the antrum, duodenal bulb and duodenal loop does not cause any CT artifacts. A small fatty density (arrowhead, CT scan) in the region of the descending colon represents an appendix epiploica. The fat (white arrows) behind the rectus muscles may simulate a mass on the B-scan. There is no evidence of any fluid between the liver and the right kidney. The root of the mesentery contains fat and is located to the left and slightly anterior to the body of the pancreas. The small bowel (jejunum) drapes toward the left side of the mesentery.

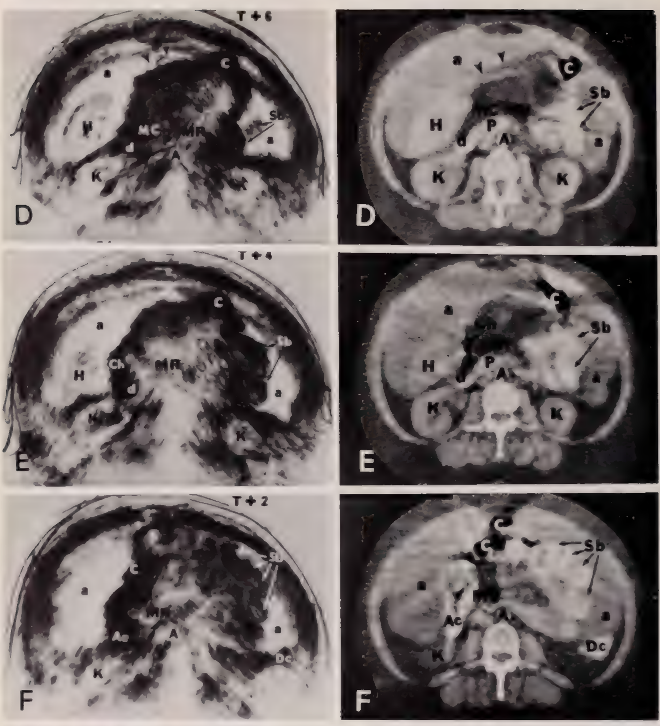

FIG 2D, 2D′. 6 cm above the umbilicus (T+6). A large amount of fluid is present above and lateral to the liver but none is seen between the liver and the right kidney. On the CT scan, contrast material is present in the descending limb of the duodenal sweep and in jejunal loops. Fat within the transverse mesocolon is continuous with fat in the mesenteric root. A portion of the gastro-colic ligament (arrowheads) can be identified. This ligament is separated from the fat in the mesocolon by a layer of fluid (anechoic in the sonogram and fluid density in the CT scan). The gas content of the distal transverse colon causes it to rise as far as the length of the mesocolon will permit.

FIG 2E, 2E′. 4 cm above the umbilicus (T+4). The mesenteric root, previously toward the left side of the abdomen, is located in the midline at this level. The mesentery is in a "standing" position due to the fat within it causing it to float.

FIG 2F, 2F′. 2 cm above the umbilicus (T+2). A large amount of fluid is present in both flanks. Multiple gas pockets are seen in the transverse colon. Small bowel loops are gathered together in a polycyclic configuration and drape over the left side of the mesentery. The mesenteric root is to the right of the midline. The mesentery itself has a vertical position with its tip bent toward the left. The grouping of small bowel loops within the mid-abdomen with ascitic fluid on each side corresponds to the classical radiological features of free fluid within the peritoneal cavity. Some contrast material has reached the retroperitoneally located ascending colon and the descending colon at this time.

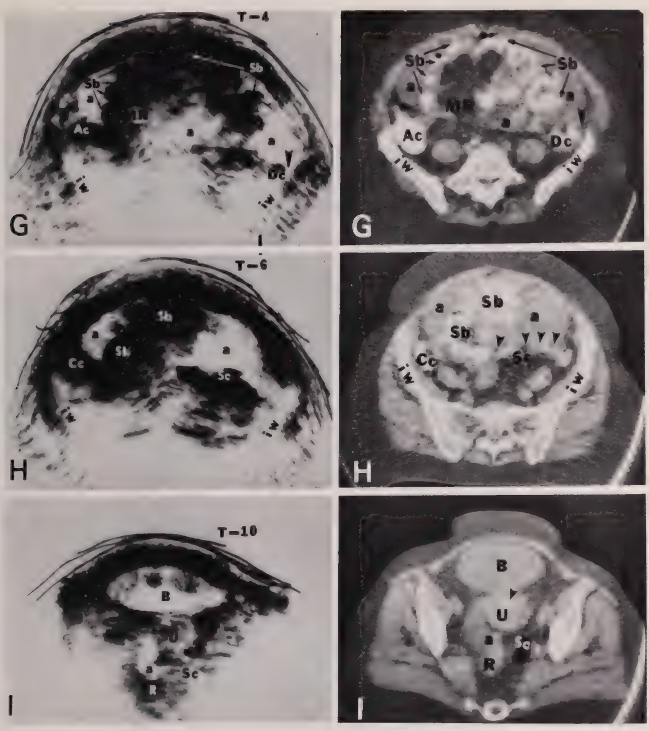

FIG. 2G, 2G′. 4 cm below the umbilicus (T−4). The lower end of the root of the mesentery is on the right side, medial to the ascending colon. Small bowel loops drape over the mesentery on each side but predominantly toward the left. Fluid in the left paracolic gutter (arrowhead) is evident in both scans.

FIG. 2H, 2H′. 6 cm below the umbilicus (T−6). This level is below the lower margin of the mesenteric root. Small bowel loops are predominantly on the right side. The sigmoid colon shows numerous appendices epiploicae (arrowheads in CT scan).

FIG. 2I, 2I′. 10 cm below the umbilicus (T−10). Fluid is present in the right side of the pouch of Douglas. The left side of this pouch is occupied by the sigmoid colon. The uterus shows a small calcification (arrowhead in CT scan), presumably within a fibroid. Gas in the sigmoid colon causes an acoustic shadow which cannot be effaced by compound scanning because of interference by the bony pelvis.

between the liver and the right kidney. This occurs because the liver is usually heavier than ascitic fluid and sinks. Therefore, unless the abdomen is so markedly distended that the liver becomes suspended by the falciform ligament, the potential space beneath the liver will not open to accommodate

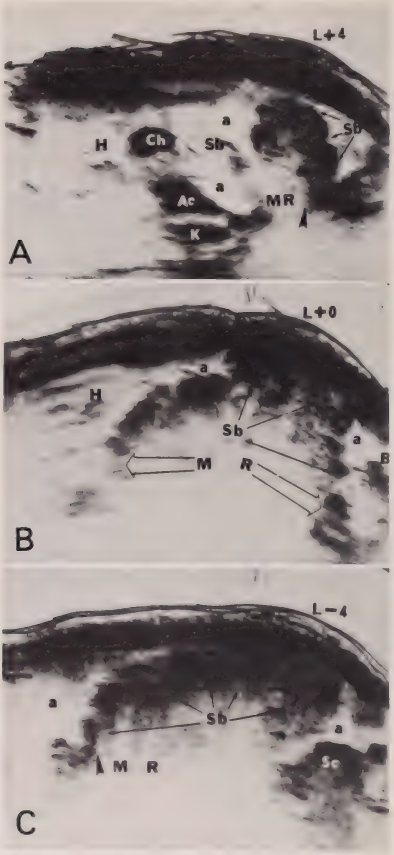

Fig. 3. Longitudinal B-scans of the abdomen of the same patient. The head of the patient is on the reader's left. Abbreviations as in figure 2.

Fig. 3A. 4 cm to the right of the midline (L+4). Fluid anterior to the liver is obscured by reverberation echoes. The hepatic flexure posterior to the lower edge of the liver and a portion of the ascending colon anterior to the right kidney are seen. The lower end (arrowhead) of the mesenteric root is present in this section. Ileal loops drape over the mesentery inferiorly, corresponding to the small bowel loops shown in Fig. 2H.

Fig. 3B. Midline (L+0). Most of the mesentery and its root is seen in this section. The "bowel" in the upper abdomen includes small bowel, transverse colon and stomach.

Fig. 3C. 4 cm to the left of the midline (L−4). The upper end (arrowhead) of the mesenteric root is evident. The sigmoid colon is present in the left lower quadrant.

fluid. Fluid was also present in the following areas: (1) lateral to the stomach and spleen; (2) over the sigmoid colon when it did not contain air; (3) in the pouch of Douglas—in the right side in this case; the left side was occupied by the sigmoid.

Since fluid produces no echoes, ascitic fluid will stand out as an echo-free area and easier to recognize on ultrasonography than CT scans. However, marked reverberation echoes may occur deep to the parietal peritoneum. If the reverberation echoes are not recognized as such, the amount of fluid will be underestimated. If fluid is minimal, the ascites may be obscured by reverberation echoes.

Collapsed small and large bowel loops and the empty stomach are highly echogenic due to numerous strong ultrasonic interfaces—serosal, intramural and mucosal. The mesentery, however, is less echogenic since fat is more homogeneous than bowel wall. The mesentery usually assumes a vertical or "standing" position in fluid due to the floating force of the fat within it. The tip of the mesentery, however, often bends to one side (usually the left) due to limitation of the peritoneal space as well as the weight of the small bowel.

The mesenteric root can be traced from its upper end, to the left of the body of pancreas, to its lower end, medial to the cecum, with the intermediate portion in an approximately longitudinal direction. Small bowel loops form polycyclic arcuate configurations around the mesentery with most draped over the left side.

Liver, spleen, stomach, small bowel loops and portions of colon are identified by both techniques. The duodenum and the distinction between individual loops of small bowel containing dilute opaque material are delineated better on the CT scans. Fat is obvious on CT scans and visceral outlines more distinct. The contrast between large fluid collections and adjacent viscera is however greater in ultrasonograms and the outlines of the viscera under these may be better defined than on CT scans.

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PEDIATRIC NOTES

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Transient Acquired Defect in Platelet Function following Therapy with AHF Concentrate

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Abstract

A case is presented of a severe hemophiliac who underwent surgical repair of a patent ductus arteriosus while receiving an AHF concentrate, Blomback type. Clinically suspected development of an AHF inhibitor necessitated administration of very large amounts of AHF concentrate to control bleeding. Further bleeding in the presence of adequate levels of AHF proved to be due to a transient defect in platelet function characterized by prolonged bleeding time, abnormal platelet factor 3 activity, and abnormal ADP-induced platelet aggregation. We postulated that this complication was caused by high levels of fibrinogen in the patient's plasma, resulting from the large amount of concentrate given. In vitro studies carried out to confirm this hypothesis were not conclusive.

Introduction

The purpose of this report is to present an unusual complication of AHF concentrate therapy—namely, the appearance of a transient defect in platelet function.

Materials

Platelet-rich plasma (PRP): Normal human blood was collected in a plastic bag containing acid-citrate dextrose (ACD) solution (one volume of ACD formula A to seven volumes of blood), and PRP was obtained by slow centrifugation at 4°C.

Plasma: Nine volumes of normal blood were added to one volume of 3.2% sodium citrate in a plastic tube. Plasma was separated after centrifugation and frozen.

Adenosine diphosphate (ADP): A stock solution of 10^{-2} M (sodium salt, Sigma Chemical Co., St. Louis, Mo.), was prepared in isotonic sodium chloride, and 0.5 ml aliquots were kept at −20°C. For the study of platelet aggregation, the solution was freshly diluted with isotonic saline. Concentrations in the text are the final values.

Fibrinogen: As described in the text.

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Methods

Factor VIII (AHF) was assayed by modification of the partial thromboplastin time (1). Factor I (Fibrinogen) was determined by the turbidimetric method of Fowell (2). Bleeding time was measured by the method of Duke (3). Platelet factor 3 activity was determined according to Hardisty and Hutton's method (4). For the measurement of platelet aggregation, changes in optical density (OD) were followed at room temperature with an Evans EEL Titrator connected to a Photovolt Linear-Log Varicord #43 Recorder. A mixture of 0.8 or 1.2 ml platelet rich plasma with 1.6 or 1.2 ml respectively of plasma, fibrinogen solution or citrated saline was placed in a cuvette. One minute later 0.3 ml of $CaCl_2$ and 0.3 ml of ADP were added. AHF Inhibitor was demonstrated using Biggs and Bidwell's method (5). Fibrinogen degradation products were measured by a tanned red cell hemagglutination inhibition immunoassay (6).

Case Report

A 22-month-old severe hemophiliac was admitted to the New York Hospital in April, 1965 for mandatory surgical repair of a patent ductus arteriosus. Over a 2-day period he received 600 units of low purity, Blombäck-type AHF concentrate (7) provided by the American National Red Cross. It contained up to 1.6 g of total protein per 100 units of AHF, of which 75% was fibrinogen. During this time, an angiocardiogram was performed without excessive bleeding. Figure 1 shows the number of units of AHF concentrate administered and the maximum level of AHF achieved. The lower graph shows the amount of protein given in the concentrate and the fibrinogen concentration in the patient's plasma.

In preparation for surgery the patient received from 200 to 600 units of AHF concentrate per day and achieved AHF levels between 30 and 115%. Surgery had to be delayed, however, because he developed a left lower lobe pneumonia. Ten days later the patient was given a total of 608 units of AHF concentrate divided in three doses over 12 hours. An AHF level of 51% was attained and the patent ductus arteriosus was ligated. During the operation excessive oozing was noticed which was well controlled by 257 additional units of AHF. Therapy was planned to maintain an AHF level between 40 and 50%.

Twelve hours postoperatively, bleeding from the chest wound was noted with a fall in the hematocrit. Packed red cells were given and a continuous drip of AHF concentrate at 80 to 266 units per hour was begun. Over the next 24 hours a large hematoma of the chest wall developed and, although AHF levels ranged between 10 and 25%, the hematocrit continued to fall. The fibrinogen level was 4.5 gm/100 ml. Thrombin time was 13.5 seconds with a normal control of 9.2 seconds. Epsilon-aminocaproic acid (EACA) and Trasylol (Bayer, Lever Kuser, Germany) were begun to counteract possible local and systemic fibrinolysis.

Five additional sutures were inserted in the chest wound and the bleeding ceased. An exchange-transfusion was performed to lower the fibrinogen level: the patient's blood was replaced by packed red cells and an AHF concentrate of greater purity, containing less fibrinogen per unit AHF (7).

During the following week very large amounts of concentrate were required to maintain adequate levels of AHF and despite this, the chest wall hematoma increased. An AHF inhibitor was suspected and on the 4th post-operative day Prednisolone and 6-Mercaptopurine were started. Splenomegaly was noted at that time; it increased over the next week and decreased slowly over the following 6 weeks.

On the 5th postoperative day oozing from the saphenous cutdown and from jugular venipunctures was first noted despite an AHF level of 50 to 60%. This persisted for 4 days. At this time (9th postoperative day) the platelet count was 300,000 and the bleeding time was more than 15 minutes on 2 occasions. Fibrinogen degradation products in the patient's serum were 72 μg/ml, (normal, less than 8 μg/ml). Five exchange transfusions were performed between the 5th and the 12th

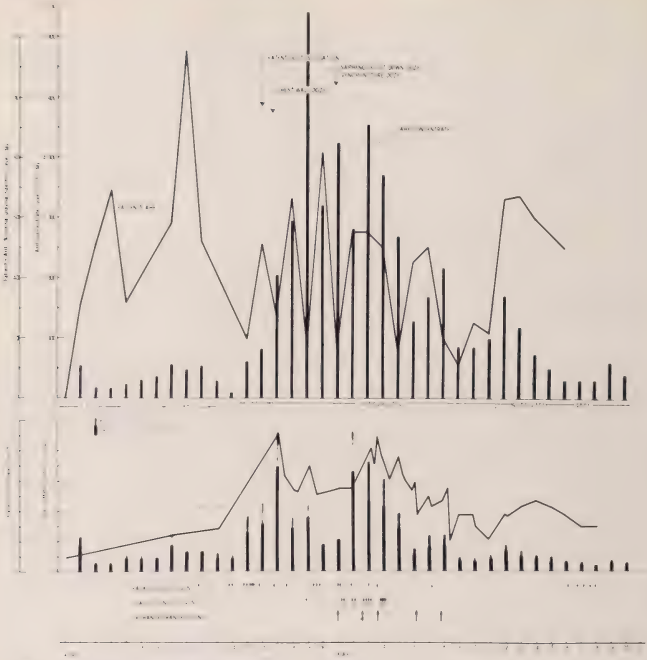

FIG. 1. Graphic representation of amounts of AHF concentrate given and levels achieved in the patient; other therapy and laboratory data.

postoperative days using packed red cells, AHF concentrate of intermediate purity, platelets and salt-poor albumin. The fibrinogen level was reduced to 1 gm/100 ml.

No further bleeding was observed as decreasing amounts of concentrate were given and finally discontinued. Bleeding time returned to normal. Prednisolone and 6-Mercaptopurine were tapered and the patient was discharged on the 30th post-operative day.

An AHF inhibitor was documented 6 weeks after discharge but was not detectable 2 months later.

In vitro studies on platelets. ADP-induced platelet aggregation in the patient's platelet-rich plasma was found to be abnormal on the 9th postoperative day. Aggregation caused by 2.5 μM ADP with 1.5 mM $CaCl_2$ was much less when 0.1 ml normal platelet-rich plasma was mixed with 0.2 ml of the patient's plasma than when it was mixed with 0.2 ml of normal plasma, indicating that an inhibitor was present in the patient's plasma. Platelet factor 3 activity in the patient's PRP was also found to be abnormal on the 9th

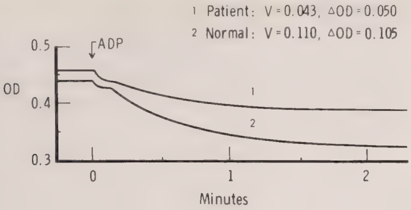

Fig. 2 ADP Induced Platelet Aggregation

(Normal PRP + patient or normal P + Ca Cl_2 + ADP)

V = slope of the steepest part of the curve, estimated as OD/min.

ΔOD = difference between the initial and the final OD

FIG. 2. ADP induced platelet aggregation in the patient as compared to a normal.

TABLE I. ADP-INDUCED PLATELET AGGREGATION

(normal PRP + patient or normal P + ADP final concentration $2.5 \times 10^{-6}M/_L$. + Ca Cl_2 final concentration $7.5 \times 10^{-3}M/_L$.)

	FIBRINOGEN OF PLASMA (mg/100 ml)	ΔOD/min (slope)	MAXIMUM ΔOD
Normal ACD Plasma	—	0.110	0.102
Normal Citrated Plasma	—	0.094	0.105
Patient's Pl. Pre-Exchange	2.9	0.066	0.072
Patient's Pl. 1h Post-Exchange	2.8	0.055	0.075
Patient's Pl. 5h Post Exchange	2.3	0.043	0.050
Patient's Pl. 10h Post-Exchange	1.9	0.077	0.073

postoperative day. Additional studies were carried out two days later, using the patient's plasma withdrawn at various times during plasmapheresis. The maximum change in optical density which was noted when 2.5 μM ADP and 7.5 mM $CaCl_2$ were added to a mixture of equal volumes of PRP and plasma was again less with the patient's plasma than with normal plasma (Fig. 2). During the plasmapheresis, there was a slight decrease in the inhibitory effect of the patient's plasma on the slope of the ADP response, and fibrinogen in the patient's plasma fell from 2.9 to 1.9 gm/100 ml (Table I).

A number of different preparations of fibrinogen were tested in vitro, including 3 preparations which had more than 87% clottable protein: one prepared by glycine precipitation (8) and two by the method of Newman et al

(9). The fibrinogen preparations were dialyzed against isotonic saline containing 0.3% sodium citrate; equal volumes of the fibrinogen or the dialyzate were added to platelet-rich plasma and tested at room temperature with concentrations of ADP between 0.5 and 5×10^{-6} μM. All fibrinogen preparations enhanced aggregation at the lower ADP concentration and had a variable effect at higher ADP concentration.

Discussion

We demonstrated a substance in the patient's plasma which inhibited platelet aggregation induced by adenosine diphosphate. Since the studies with platelets were carried out at room temperature, aggregation rather than release was inhibited (10).

The nature of this inhibitor was not well defined. Prolongation of the thrombin time in association with high levels of fibrinogen and increased fibrin split products were present in the patient reported here and may have contributed to the bleeding he developed in face of adequate levels of AHF. Increased amounts of fibrin split products are known to interfere with platelet function (11) and to prolong the thrombin time (12).

Bark and Orloff (13) have reported a patient with prolongation of the PTT and thrombin time following AHF infusions; they suggested that large quantities of fibrinogen or other inhibitors in the AHF concentrates given to the patient were responsible for the clotting abnormalities observed. Platelet studies, however, were not done.

Hathaway et al (14) recently reported a patient who developed a postoperative bleeding diathesis on two occasions, both times following intensive therapy with cryoprecipitates and in the presence of adequate levels of AHF. Bleeding in this patient ceased when glycine precipitated VIII concentrate was given, and fibrinogen level that had been 1307 mg/100 ml fell to levels under 500 mg/100 ml.

We performed in vitro studies to verify whether high levels of fibrinogen could be responsible for the transient defect in platelet functions. Our results were not conclusive.

Whatever the reason for the bleeding tendency that can occur in transfused hemophilic patients, the use of more highly purified AHF concentrates seem to be an appropriate indication in situations where the need for large amounts of the product can be anticipated.

Acknowledgments

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NEUROLOGIC-NEUROSURGICAL NOTES

MARTIN H. SAVITZ, M.D. AND ALLAN E. RUBENSTEIN, M.D., COEDITORS

Repair of Postoperative Cerebrospinal Fluid Leak following Radiation and Laminectomy: A Case Report

Submitted by

EDGAR ALTCHEK, M.D., VED P. SACHDEV, M.D., AND LEONARD I. MALIS, M.D.

Abstract

A 33-year-old male patient treated with radiation therapy for a spinal cord astrocytoma developed cerebrospinal fluid leak after secondary laminectomy. Repair of the leak with bilateral transposed pedicle muscle flaps is discussed.

The hazards of infection accompanying cerebrospinal fluid leak after spinal surgery are well known. The purpose of this paper is to report successful surgical repair of a case complicated by radiation necrosis in which conventional methods of treating a postoperative cerebrospinal fluid fistula were inadequate. The type of approach employing muscle and skin flaps has not previously been described in the neurosurgical literature.

Case Report

A 33-year-old male presented with the insidious onset of left lower extremity weakness which progressed over a 15-month period. Diagnostic studies including myelography were consistent with an intramedullary mass. The patient underwent a decompressive laminectomy from T4 through T8 at another hospital. An enlarged spinal cord was visualized; no evidence of syringomyelia was found and biopsy was not taken. The operative impression was an infiltrating tumor of the spinal cord. Postoperatively, the patient received 6,000 rads of radiation limited to the area of the widened cord seen at the time of surgery. After an interval of temporary improvement the patient's condition deteriorated and he was transferred to Mount Sinai Hospital for further workup and treatment.

Neurological examination on admission to Mount Sinai Hospital revealed markedly spastic gait, severe weakness of lower extremities, more obvious proximally than distally, and bilateral ankle and patellar clonus. Deep tendon reflexes in the lower extremities were exaggerated. Bilateral Babinski signs were present. There was hypesthesia and hypalgesia in the right lower extremity up to the T12 dermatome. Posterior column sensations and bladder and anal sphincter functions were normal.

Pantopaque myelography demonstrated a complete block at T6 with widening of the spinal

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cord from T6 through T12. Laminectomy from L1 to T8 and reexploration of the lower part of the previous laminectomy at T6, T7 and T8 were performed. The pia and arachnoid mater were thickened and adherent at multiple levels even below the level of the previous surgery and the spinal cord was markedly widened from about T12 to T8. At T8 there was a remarkable sudden shrinkage of the spinal cord to almost normal size representing the lower limit of the radiation field. Since the cord below T8 was apparently excluded from the radiation portal the tumor had apparently continued to grow and expand in that area; the maximum widening was around T10 and T11.

Microsurgical myelotomy and biopsy of the infiltrative tumor was performed; histology of the tumor was reported as astrocytoma. Because of spinal cord swelling, the dura mater could not be closed and a siliconized Dacron graft approximately 20 cm. x 3 cm. was tacked to the dural edges as an artifical membrane. The wound seemed to be healing well for one week before cerebrospinal fluid leaked through a pinhole opening in the lower part of the incision of previous laminectomy. Closure of this small area with skin sutures, repeated spinal taps and nursing the patient in a head down position failed to prevent break down of the skin and an active cerebrospinal fluid leak recurred after three days. Because of profuse cerebrospinal fluid drainage the laminectomy incision was reopened; necrotic material from the paravertebral muscles was debrided. After freshening of the edges of the skin and fascia a primary closure was again attempted, repeated spinal taps and nursing in a slightly head down position continued, but the cerebrospinal fluid leak did not stop.

One week later the patient was again taken to the operating room and the entire site of previous laminectomy and irradiation area was reopened. An extensive radiation necrosis was encountered extending from the skin to the spinal cord and involving paravertebral muscles bilaterally. Friable necrotic tissue was resected and the previously introduced dural graft was removed. Clear cerebrospinal fluid was seen to be coming freely from around the spinal cord. The radionecrotic skin and underlying damaged tissue, including nonviable paravertebral musculature, were widely excised to an area of well-vascularized tissue. Bilateral superiorly based paravertebral muscle flaps were raised and transferred into the spinal defect in order to cover the exposed spinal cord, provide

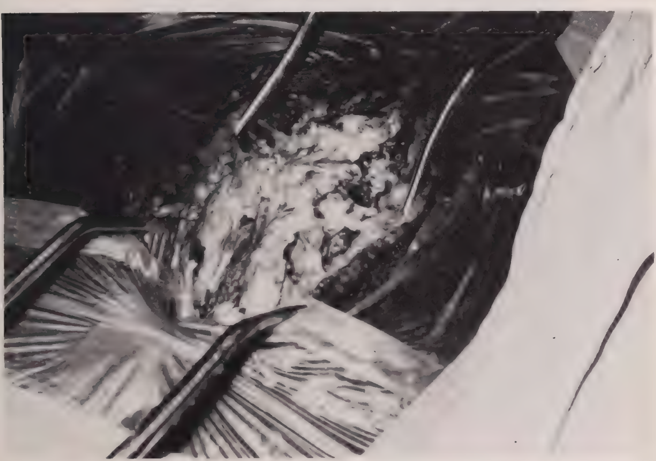

FIG. 1. Operative photograph of the opened laminectomy wound showing cheesy, necrotic tissue filling the wound.

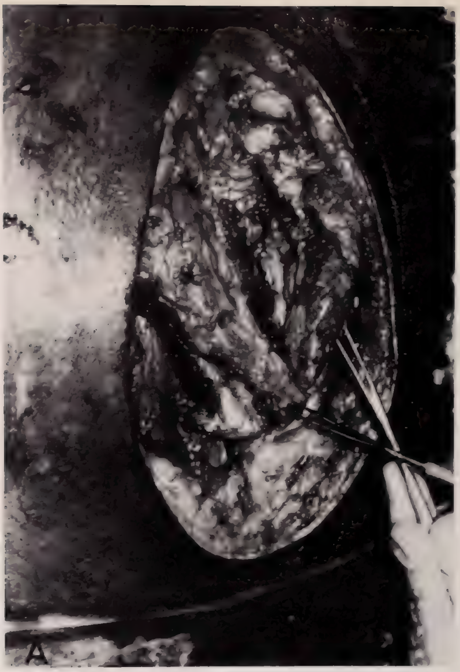

FIG 2a. Operative photograph showing apposition of the transposed muscle flaps.

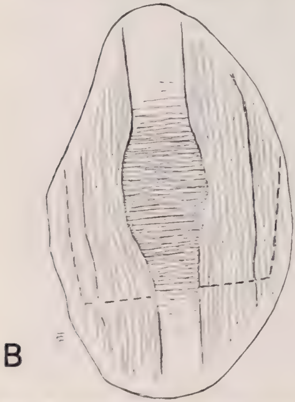

FIG. 2b. Diagrammatic representation of operative area after debridement. Dotted line shows muscle incision.

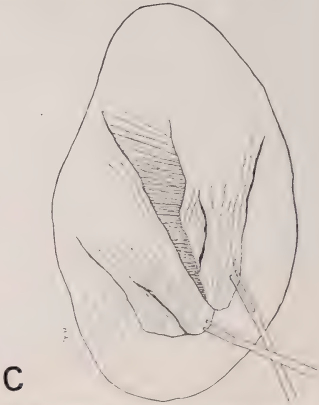

FIG. 2c. Diagrammatic representation of Figure 2a.

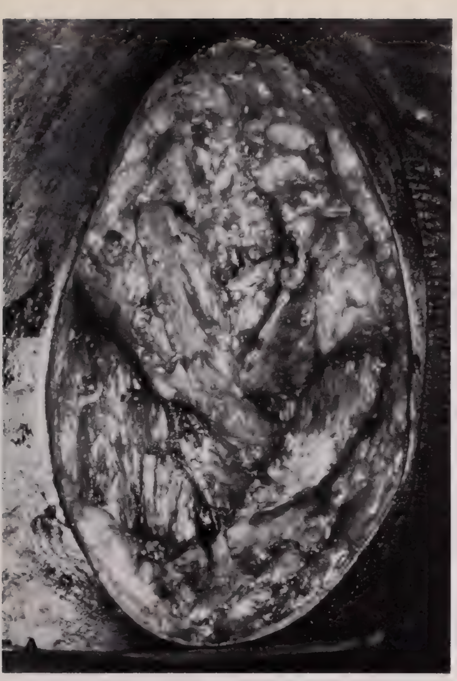

FIG. 3a. Operative photograph of the sutured transposed muscle flaps.

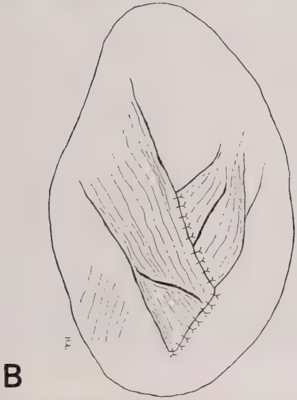

FIG. 3b. Diagrammatic representation of Figure 3a.

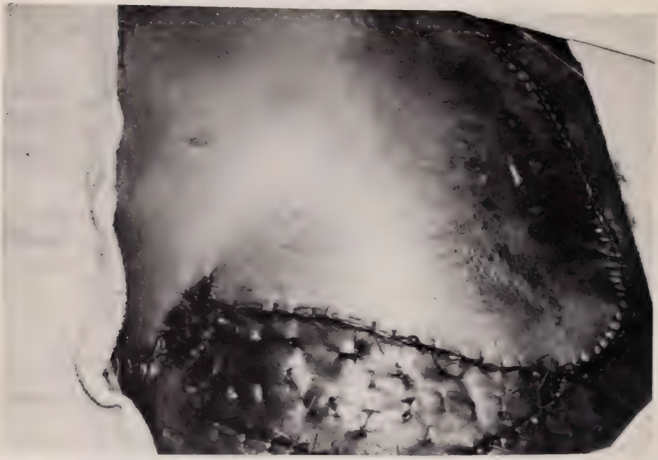

FIG 4. Completed closure with skin rotation flap and split-thickness skin graft to flap donor site.

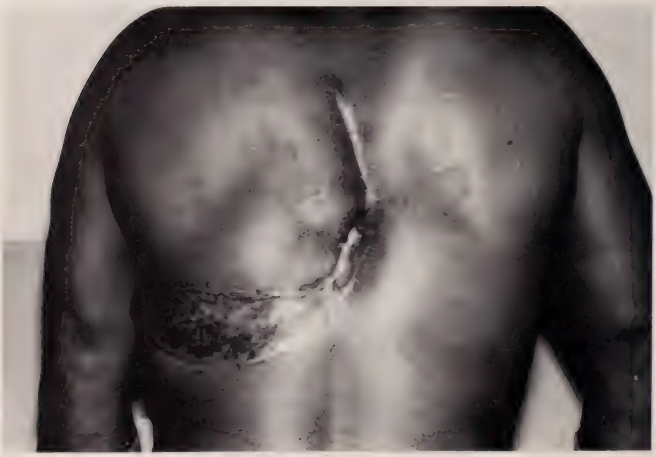

FIG. 5. Healed wound six weeks later.

improved blood supply and seal the cerebrospinal fluid leak. The skin defect was repaired with a large rotation skin flap from the scapular region and the flap donor site resurfaced with a split thickness skin graft.

The patient was again nursed in a slightly head down prone position. Postoperatively, there was progressive diminution in the amount of cerebrospinal fluid leakage until it ceased completely two weeks after the last surgery. During a period of five years of follow-up, the wound has remained stable with no recurrence of the cerebrospinal fluid fistula. No further radiation has been given. Patient has slowly and steadily deteriorated neurologically.

Discussion

Conventionally, minor cerebrospinal fluid leaks after spinal surgery can be treated by skin suturing, sometimes assisted by repeated spinal taps and nursing in a prone position with the head slightly down to reduce the fluid pressure-head in the region of the laminectomy. In more sustained cerebrospinal fluid leaks, reoperation with adequate watertight closure of the dura and closely approximated layered closure of the wound may be necessary. If local wound infection is contributing to sustained cerebrospinal fluid leak, debridement of nonviable infected tissue assisted by adequate antimicrobial cover and proper closure of the wound helps to close the fistula. McCoy (1) has, on his experiments with dogs, shown that the presence of an active cerebrospinal fluid leak does not inhibit the healing process; to the contrary, fibroblastic proliferation seems to be accelerated. However, for healthy granulation tissue to form, a base of well vascularized tissue is essential. In our own case after adequate debridement, the normal healing process could not occur because of the relatively avascular area created by resection of radionecrotic tissue.

Various types of diversion techniques have been used to accelerate healing by keeping the site of the leak dry and by reducing the fluid pressure-head. White et al (2) used a closed external ventricular drainage system which they termed as "externalized fifth ventricular drainage system." All 51 of their valve-modulated externalized ventriculostomies in 33 patients were performed on patients requiring drainage for acutely raised intracranial pressure; in their series there were no postoperative cerebrospinal fluid fistulae. McCallum et al (3) reported a modification of White's method (2) using a continuous lumbar drainage in nine patients and a continuous ventricular drainage in three patients with postoperative cerebrospinal fluid leaks. Four of the nine patients with lumbar drainage had undergone laminectomies followed by pseudomeningocele formation and cerebrospinal fluid leaks; all these leaks stopped after lumbar thecal drainage. Vourc'h (4) reported a similar case in which a cerebrospinal fluid leak occurred after spinal surgery. His patient had also been irradiated. By inserting a catheter through the occipital region and establishing continuous cerebrospinal fluid drainage and postoperative care of the patient in an adequate Trendelenburg position, he was able to stop the cerebrospinal fluid leak in a 15 day period.

In all patients where diversion techniques are successful, a prerequisite for satisfactory wound healing is the presence of an adequate granulation tissue reaction in a reasonably vascularized bed; such tissue in our patient was grossly lacking because of the massive radiation necrosis. Rosenthal et al (5) described a technique for closure of a cerebrospinal fluid leak utilizing local muscle approximated over the spinal defect with wide deep tension relieving sutures, thereby creating watertight seal. Because of the extensive tissue damage in our patient, local musculature was not available to approximate over the cord. The large defect resulting from the debridement of the skin and deep tissues devascularized by radiation was repaired with bilateral transposed pedicle muscle flaps from the paravertebral regions thereby furnishing healthy, well vascularized tissue to the poorly nourished laminectomy site. Primary closure of the surface defect was accomplished by means of a skin rotation flap. This procedure provided sufficient healthy tissue to allow complete healing of the wound and the cerebrospinal fluid fistula.

Summary

A 33-year-old male patient treated with radiation therapy for a spinal cord astrocytoma developed a cerebrospinal fluid leak from his laminectomy incision following surgical reexploration and biopsy.

The versatility of pedicle muscle flaps in the repair of problem defects is well documented in the literature (6–11). To our knowledge this is the first reported case of the use of muscle transposition flaps in the surgical management of a cerebrospinal fluid fistula.

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THE STUDENT'S CORNER

JONATHAN STEINBERG, B.A., EDITOR

This column is a forum for medical students to comment on issues concerning medical school and medical education. The editor of this column is a third-year medical student and elected student representative at Mount Sinai School of Medicine of The City University of New York. Mount Sinai School of Medicine students are invited to take advantage of this opportunity to reach a wide and influential readership. Medical students from other schools are also invited to contribute.

Contact Mr. Steinberg through Mount Sinai School of Medicine, The Annenberg Building, Room 13-98A, Fifth Avenue and 100 Street, New York, N. Y. 10029. If you do not have time to write an entire column, you still can contact Mr. Steinberg and share your thoughts on a particular topic which perhaps can be incorporated into a future column.

David A. Dreiling, M.D.
Editor-in-Chief

Pass-Fail—A Medical Student's Perspective

Submitted by

DAVID S. JACKSON, B.A.*

Medical schools across the country use a variety of methods in the evaluation of student performance. Some use a numerical or letter grade approach; others adhere to the pass-fail philosophy; and still others employ modified systems. Proponents of the traditional approach point to the necessity for objective discrimination among students for placement following graduation. They believe that a grading system stimulates motivation and encourages academic excellence. On the other hand, those favoring a pass-fail system deplore the needless competition and tension among students that a traditional approach promotes. They refer to the studies which have indicated that grades are not proper predictors of future achievement (1–3). As a second-year medical student at Mount Sinai School of Medicine, I have a keen interest in this continuing debate, especially since Mount Sinai is currently reviewing its policies toward grading.

Since its inception, Mount Sinai has used a modified pass-fail system. During the first two years of basic sciences, students are anonymously evaluated on a pass-fail basis, only those failing being identified. During the clinical years, an honors-pass-fail system is employed. Written evaluations by preceptors, house staff members, and departmental chairmen are compiled as each student progresses through the four years. Mount Sinai has been successful with this type of student assessment. An article by Dr. Barry Stimmel, Associate Dean for Academic Affairs at Mount Sinai, upheld the achievements of the school's modified pass-fail system and effectively revealed that critics of the system simply do not have the facts to support their claims. He concludes that, "a traditional grading system is unnecessary for either detecting superior students or predicting a student's subsequent performance as a house staff officer" (4).

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* The author is a second-year student at Mount Sinai School of Medicine of The City University of New York.

The subject is both complex and controversial, worthy of further critical review and appraisal. However, as a student who has been experiencing what pass-fail really means, I would like to discuss how this grading system has affected both me and my classmates. As mentioned above, the method of student assessment which exists during the years of basic sciences differs from that used during the clinical years. A strict pass-fail approach remains intact exclusively during the years of basic sciences, and it is only in reference to these years that I am concerning myself. The most important effect of the pass-fail system at Mount Sinai has been the reduction of competition and tension among students. Pass-fail has created an amicable and relaxed atmosphere. In short, students worry less. This is the primary goal of a pass-fail system, and at Mount Sinai this goal has been successfully attained. Medical school can be a difficult and frustrating experience for any individual. The number and variety of 'itises' and 'opathies,' 'omas' and 'emias,' 'isms' and 'osises' present an extraordinary volume of knowledge for the student who must learn them. To drive a student's mind by introducing the competition of grades would make learning an even more difficult process. Medical students are by nature individuals who will study and who will learn, because medicine is what is important to them. Medical students have been processed through a stringent selection procedure. They have proved that they possess the desire, motivation, and commitment necessary to study medicine. With such highly motivated individuals, grades are a hindrance, not an asset, to learning.

Although the study of medicine requires a total commitment from the student, studying medicine should not be an all-consuming process. Medicine is the vocation of every medical student, but it need not be his pasttime in addition. To learn every detail of every anomaly, syndrome, disease, and deficiency is simply an impossibility. Indeed, complete lifetimes have been devoted to the endless pursuit of medical knowledge. There is more to being a physician than possessing the ability to store and recite innumerable medical facts and theories. To be a complete individual involves the realization that medicine is not everything. I enjoy medicine and learning about medicine. I spend many hours in class and many more studying course material. Yet, I am able to pursue nonmedical activities as well. These activities are as important to me as is studying medicine, and in this respect, I believe that the pass-fail system has played a significant role. By reducing pressure and anxiety it has allowed me to pursue these activities without having to worry that I would jeopardize my competitive position in my class. It has given me freedom and a "peace of mind" that I never thought possible when I first began medical school.

With reduced emphasis upon grades has come increased emphasis on the pursuit of personal interests in medicine. Mount Sinai offers a multitude of structured and unstructured elective programs. The pass-fail system fosters personal involvement in these programs. I have been able to investigate aspects of medicine which are of particular interest to me, and I believe most students in my class have taken similar advantage of this opportunity.

In mentioning my experiences with pass-fail, I am aware that I dwell upon subjective criteria. This is my intention, for I believe many, both critics and advocates of the pass-fail philosophy, undervalue the importance of these aspects. Past research which has delved into the advantages and disadvantages of various forms of grading systems has too often emphasized objective criteria such as performance on the National Board examinations. Perhaps more weight should be given to the psychological advantages that a particular system affords, something which at present is difficult to quantify. To this end, pass-fail would clearly demonstrate its superiority.

Many of my fellow students and I, though cognizant of the positive attributes of a pass-fail system, have encountered some of the problems associated with it. First and foremost is the fact that, in the absence of grades, subjective faculty evaluations have assumed a greater role in overall student assessment. In addition to pass or fail on objective examinations, each student assessment includes a narrative critique based on clinic, laboratory, and conference performance. Students have thus become apprehensive about how they should be conducting themselves during their interactions with faculty members. Concern over the relative importance of subjective versus objective criteria in student assessment has also emerged. The structure of Mount Sinai's objective pass-fail system during the first two years is such that students are not judged with respect to one another. Yet, if students are ultimarely judged according to subjective written evaluations, the usefulness of a pass-fail system is apparently negated. At any institution which utilizes a pass-fail approach, this poses a legitimate cause for concern. At Mount Sinai, this concern has been largely mitigated through the integrity of faculty-student relationships. The Office for Student Affairs at Mount Sinai is knowledgable and responsive to the needs and concerns of medical students. Nonetheless, the element of doubt concerning the subjective "grading" of students continues to exist and is surely the chief problem associated with a pass-fail grading system.

Other problems with pass-fail have also surfaced. For instance, since students are identified only when they fail, those who pass are unaware of their standing with respect to their peers. This is a particularly vexing problem for some students. Nevertheless, any solution would probably involve a diminution in anonymity, a feature of the current system which plays a prominent role in keeping competition at a minimum.

Another complaint is levied by some of those who continually perform well on the objective examinations. Since the pass-fail system does not correlate names with scores, their excellence cannot be appreciated. However, those students for whom this is a problem are precisely the students who do not reap the full benefits of a pass-fail system. These students will be highly competitive and pressure driven no matter what type of grading system is used. Pass-fail is just not for them.

In conclusion, as a student who is familiar with a pass-fail grading system, I support both the concept and its practice at Mount Sinai. It has helped make medical school a more pleasurable and worthwhile experience for me. I believe that I will be a better person, and, ultimately, a better physician because of it.

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Student Section

Pediatric Burn Care: 1973–1975

JUAN ORELLANA, B.A.

Abstract

A study of pediatric burn fatalities during 1973, 1974 and 1975 in New York City was undertaken. Data was compiled with attention to demographics, boroughs, factors causing burns, type of burn, percentage body burn, place and duration of hospitalization if any. The results indicate that the hospitals of New York City are unable to deliver good burn care.

This present study attempts to look at the pediatric burn fatalities during 1973, 1974, and 1975 within New York City. Particular attention was paid to the distribution of cases by borough, sex, age, ethnic groups, site of injury, factors causing burn, type of burn, percentage body burn, place and reason for death, length and site of hospitalization.

Methods

The fatalities were taken from the Medical Examiner's Office files of people that died in fires occurring in public places, private homes and multiple family dwellings in New York City during the three-year period from 1973–1975. Also included were suicides by fire, child abuse deaths and deaths from smoke inhalation. All children nineteen years of age and under were included.

All cases were documented by one or more of the following: hospital report, medical examiners' report or fire marshall's report. From each patient's file the following data was obtained: name, address, borough where the injury occurred, factor causing burn, type of burn, site(s) of burn, percentage of body burned, procedures performed (such as tracheostomy, intubation, escharotomy, fluid replacement, blood transfusions, cardiopulmonary rescusitation) date of death, and hospital where death occurred. If any data was unobtainable from the patient's file it was marked "not recorded."

The probability of survival corresponding to age and percentage body burned for each case was added and the expected number of deaths for such a series calculated. This was compared to the actual number of deaths encountered in this series.

The individual bits of data for each case were recorded and added in order to obtain any trends within this series.

Results

During the three year period seventy-one children perished in New York City fires. For the overall three-year period and in any given year the number of female fatalities exceedes that of the males (Table I). Brooklyn had the

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From Mount Sinai School of Medicine of The City University of New York, N. Y. 10029, submitted in partial fulfillment of the Third-Year Clerkship requirement for the Department of Surgery. Mr. Orellana is currently a fourth-year medical student.

TABLE I

Distribution of Burn Fatalities by Sex, 1973–1975

	MALE	FEMALE	TOTAL
1973	7	12	19
1974	15	20	35
1975	5	12	17
TOTAL	27	44	71

TABLE II

Distribution of Burn Fatalities by Borough, 1973–1975

	MANHATTAN	BROOKLYN	QUEENS	BRONX	STATEN IS	OTHER	TOTAL
1973	3	11	3	1	0	1	19
1974	6	22	4	2	1	0	35
1975	4	7	3	1	2	0	17
TOTAL	13	40	10	4	3	1	71

most deaths recorded for the period studied (forty cases) (Table II). Twenty-seven females and twenty males were between one and six years of age; thirteen females and five males were between seven and twelve years of age and four females and two males were between seventeen and nineteen years of age. Eleven victims were hispanic, eighteen were Caucasian, thirty-six were black and the remaining six were not recorded.

Twelve cases occurred in an unrecorded location (16.9%), sixteen cases in a single family dwelling (22.5%), forty-two in a multiple family dwelling (59.2%) and one case in a public facility (1.4%).

Thirty-seven of the cases had no factor causing the burn listed (52.1%), while eleven cases were attributed to arson (15.5%), three cases to faulty wiring (4.2%), and twenty cases to accidents (28.2%) such as playing with matches, reaching across a lighted stove, etc.

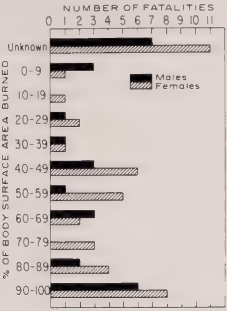
Eighteen cases did not have the location of the burn injury recorded (25.3%), seventeen had ocular involvement (23.9%), forty-four had trucal involvement (62.0%), forty-three had head and neck involvement (60.6%), thirty cases had unilateral or bilateral hand involvement (42.3%), thirty-eight had unilateral or bilateral lower limb involvement (53.5%) and twenty-four cases had other and unspecified parts involved (33.8%).

Forty cases suffered some third degree burns (56.3%), twenty-five suffered second-degree burns (35.2%), two cases had first-degree burns (2.8%) while for twenty-four cases (33.8%) the degree of burns was unrecorded.

The body surface area burned for each case was calculated from the medical examiner's records and the hospital's houseofficer report. The information was standardized using the Lund and Browder percentage burned chart (1) which takes into consideration the child's age when computing burn area. Table III

TABLE III

Distribution of Body Surface Area Burned (Males & Females), 1973–1975



depicts the body surface area burn distribution for males and females. Whereas the males suffered more burns to the upper half of the body, the females tended to have a more uniform distribution to their burns.

Twelve cases had the place of death unrecorded (16.9%), seven died at the place of injury (9.9%), thirty-two died in the hospital (45.1%) and twenty were listed as dead on arrival (28.2%).

Many factors contributed to the burn fatalities. Forty-one cases were attributed to carbon monoxide poisoning (57.7%), four cases to respiratory tract injury (5.6%), one case to renal failure (1.4%), four cases to sepsis (5.6%) and fifty-one cases had toxemia of the burn listed as contributing to their deaths (71.8%). In sixteen cases the cause of death was unrecorded (22.5%). Two children had a prior burn history. Another child had an elevated alcohol content of 0.3% in a blood sample taken for toxological examination.

A total of thirteen patients required hospitalization for longer than twenty four hours before death occurred. This represents 40.6% of the total number that died in the hospital.

Discussion

Burns in children stem from parent carelessness, a child's innate curiosity and accidents (2, 3); moreover, a potentially small burn may result in a massive burn in the child that wears flammable clothing (2). Children have now become victims of an arsonist's rage and the punching bag of emotionally unstable parents (4).

Children for the most part have a good rate of survival; this excludes the very young (5–7). Yet this study demonstrates that given the percent body surface area burned and age for each case in this series, more children died than was expected. For this series thirty-five patients were expected to die from their burns, yet this series totals seventy-one fatalities. It is a shame that a child with a thirty percent body surface area dies in a community hospital before being transferred to a burn unit or a general hospital equipped to handle such a burn. Since only forty-two beds were assigned to burn management in New York City during the period studied, it was difficult to place many patients in a burn unit. In this study only two of thirteen patients dying after a twenty-four hour hospitalization died in a burns unit. Both cases had a body surface area burn of greater than sixty percent.

Some factors affecting burn mortality rate are full thickness body surface area burn, size of burn, age of patient, occurrence of pulmonary or cerebral complications and shock in the post burn period (8–11). This study points out that half of the New York fatalities should not have occurred. It was also found that girls tended to sustain a greater body surface area burn, probably because of their loose garments acting as a chimney for the flames. In addition, carbon monoxide poisoning, sepsis and respiratory tract injury still contribute significantly to burn mortality and, finally, that in 71.8% of patients death was in addition to other causes attributed to burn shock. No mortalities were attributed to scalds which usually shows a better survival rate than flame burns.

Alcohol intoxication is incriminated as causing a predisposition to burns in adults (9, 12). The fact that more and more children take drugs or alcohol at younger ages should now be included as a factor predisposing children to burns. This is evidenced by the one case in this series. The child was an eight-year-old female whose parents were known to the admitting hospital as chronic ethanol abusers. The child was left at home alone and the fire which claimed her life was attributed to her playing with matches. Toxologic analysis of her blood by the medical examiner demonstrated an elevated ethanol level.

The city needs an additional burn facility where treatment and research coincide. New York City's financial pains have decreased burn unit personnel significantly. Burn care is a group effort by specially trained personnel and suffers when personnel are forced to do jobs with which they are unfamiliar.

Burn education is lacking on many levels. Children should be taught how to correctly react to a fire. A child whose clothes have ignited should not start running and spread the flames. House officers should be educated in burn therapy, and the art of handling both the medical and surgical aspects of a burn case.

A burn institute would be invaluable in New York City. It would provide educational programs, rehabilitation, data organization (thus helping to eradicate those categories marked "not recorded" in this study). This study has attempted to point out that data on burned patients in a major city is poor and that the results of the Shriner Institutes or Brooke Army Center can not be duplicated in New York City at this time.

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Primary Pontine Hemorrhage: Correlations of Pathologic Features with Postmortem Microangiographic, and Vertebral Angiographic Studies

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Although the pathologic and neurologic findings in cases of primary pontine hemorrhage have been well described (2, 7–11), there has been little correlation with postmortem microangiographic study, vertebral angiography and computerized tomography.

This report is a comparative study of 23 autopsy cases of primary pontine hemorrhage, 11 of which underwent postmortem injection study, 19 vertebral angiography and one computer assisted tomography.

Materials and Methods

During the last seven years from April 1969 to April 1976, autopsy was performed in 104 cases with cerebral hemorrhage at the Akita Research Institute of Brain & Blood Vessels. Primary pontine hemorrhage was found in twenty-three cases (Table I). The ages of the patients range from 33 to 67 years, averaging 50.3 years. There were 19 males and 4 females. Surgical interventions were made in 8 cases; continuous ventricular drainage in 6 cases, removal of intrapontine hematoma in one and ventriculo-atrial shunt in one. Injection studies were performed on 11 cases using 10% aqueous suspension of Micropaque (Damancy Ltd., England) after removal of the brain. The injected specimens were then cut into slices of two mm thick in horizontal planes in 8 cases and in sagittal planes in 3 cases. Each slice was radiographed with the aid of ultra-soft x-ray (Nippon Softex Co., Tokyo).

In 19 cases, vertebral angiography was performed within 24 hours after the onset of symptoms either by transfemoral catheter technique or by retrograde brachial artery injection. Of these angiotomography was performed in 5 and computer assisted tomography (EMI scanner) in one.

Results

Clinical aspects of the cases: The clinical pictures of 23 cases are summarized in Table II. All cases were admitted within 13 hours from the onset of the illness. Neurologic and clinical manifestations on admission were as follows:

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TABLE I

Summary of Cases

Case	Patient no.	Name	Age	Sex	Autopsy no.	Inj. study	VAG
1	69-1520	T. S.	57	M	20-69		○
2	69-1519	H. S.	44	M	21-69		○
3	70-437	K. N.	48	M	6-70		○
4	70-365	N. O.	64	F	12-70		○
5	70-949	Z. S.	44	M	20-70		○
6	70-1532	R. M.	55	M	43-70		○
7	71-534	F. S.	59	M	13-71		
8	71-966	T. S.	53	M	30-71		○
9	71-1580	K. O.	33	F	43-71		
10	72-773	H. N.	55	M	28-72	○	○
11	70-1420	K. N.	41	M	E2-72		○
12	71-974	T. K.	46	F	28-73		○
13	73-1556	Y. S.	60	M	43-73		○
14	73-1703	K. S.	44	M	52-73	○	
15	74-576	T. K.	33	M	12-74	○	○
16	74-596	T. S.	54	M	17-74	○	○
17	71-252	H. O.	48	M	28-74	○	○
18	74-1253	R. I.	50	M	31-74	○	○
19	74-1818	K. F.	57	M	46-74	○	○
20	75-87	T. I.	42	M	3-75	○	
21	75-322	I. K.	67	M	13-75	○	○
22	75-1099	A. T.	59	F	35-75	○	○
23	75-918	K. K.	45	M	8-76	○	○
Mean: 50.3 y.	M	19 cases			11 cases	19 cases within 24 h from onset	
	F	4 cases					

(1) abrupt onset of coma in 100% of all 23 cases, (2) miotic pupil or anisocoria in 72%, mydriasis in 18.2%, and normal sized pupil in 9.1%, (3) quadriplegia in 100%, (4) hyperthermia in 81.8%. (5) The CSF was bloody in all of 18 examined cases, and (6) preexisting hypertension including in 18 cases (85.7%) one case of toxemia of pregnancy.

Duration of illness from onset to death varied; within 24 hours (21.7%), 48 hours (34.7%), 7 days (52%), and 14 days (69.4%). Exceptionally long survival for more than 34 days, with the longest survival of 2 years and 78 days, was seen in 4 cases under adequate control of respiration.

Macroscopic observations of the specimens: The locations of the hematomas of the 23 cases are shown in Fig. 1.

Moderately large hematomas were located mainly in the mid-pons (Fig. 1, 2, 7E); twelve of 23 were localized in the tegmentum of the pons but 11 involved almost the entire pons. The extent of the hematomas was relatively symmetrical (Fig. 1, 3, 5). Rupture of the hematoma into the fourth ventricle was seen in 20 cases: in 17 of the 20 cases, the fourth ventricle was somewhat enlarged and filled almost completely with hematoma; and in 11 of these 17 cases, the hematoma also filled the aqueduct, third ventricle and foramen of Magendie. The roof of the fourth ventricle and lower aqueduct were displaced backward and upward to varying degrees, resulting in posterosuperior displacement of the precentral cerebellar and preculminate fissures of the superior vermis. The

TABLE II

Clinical Summary

Case	Age	Sex	Duration from Onset to Admission	Duration from Onset to Death	Initial Symptoms & Clinical Course (Duration lapsing into coma.)	Neurological & Clinical Manifestations on Admission								Preexistent Hypertension	Surgical Intervention (Time after onset) h.:hour d.:day
			m.:minute, h.:hour, d.:day, y.:year			Consciousness	Pupil Light Reflex	Motor Involvement	Deep Reflex	Temperature over 39°C (◎: over 40°C)	Blood Pressure	CSF	WBC		
1	57	M	4-10h.	1d19h-2d1h	suddenly onset of unconciousness (coma)	coma	pinpoint(l.l) sluggish	tetraplegia	↑	◎	130/100	bloody	20,500	○	Evacuation of the hematoma (26h.)
2	44	M	1h.	18d.	suddenly onset of unconsciousness (coma)	coma	pinpoint sluggish	tetraplegia	↓	○	200/ 90	bloody	10,400	undetermined	
3	48	M	5h.	2d3h	vertigo → headache, vomiting → coma (3h.)	coma	mydriasis absent	tetraplegia	↓	○	176/ 78	bloody	16,700	○	
4	64	F	8h.	53d.	disturbance of consciousness → coma (5m)	coma	pinpoint absent	tetraplegia	lt. ↑		130/ 60	bloody	10,000	○	
5	44	M	3h.	13d.	numbness in lt.leg → convulsion → coma (2-3m)	coma	anisocoria (rt.pinpoint) lt.absent rt.sluggish	tetraplegia	↑	◎	164/	bloody	9,100	○	
6	55	M	2h.	14h.	numbness in lt.hand → dist. of consciousness → coma (1h.)	coma	pinpoint absent	tetraplegia	↑	◎	2[illegible]0/120		[illegible]	(—)	
7	59	M	3h.	7d.	headache → nausea, vomiting → lt.hemiplegia → coma (10m.)	coma	pinpoint present	lt.hemiplegia ↓ 1d tetraplegia		○	184/110		13, 00	(—)	
8	53	M	10h.	34d.	headache, vomiting, dysarthria → coma (3h.)	coma	anisocoria (rt.pinpoint) absent	tetraplegia	↑	◎	150/ 80	bloody	13,100	○	
9	33	F	1h.	16h.	dyspnea → coma (sudden)	coma	mydriasis absent	tetraplegia .	↑		210/140	bloody	15,100	○ toxemia of pregnancy	
10	55	M	13h.	2d10h	dist. of consciousness → salivation → coma (15m.)	coma	anisocoria (lt.mydriasis) absent	rt.facial palsy (?) tetraplegia	rt. ↓	◎	120/ 96	bloody	12,000	○	continuous ventricular drainage (17h.)
11	41	M	4h.	1y120d	headache → coma (20m.)	coma	pinpoint sluggish	tetraplegia	↑	◎	130/ 75	bloody	6,300	(—)	ventriculo-atrial shunt (14d.)
12	46	F	1h.	2y78d	dist. of consciousness → vomiting; coma (1-2m.)	coma	normal size prompt	tetraplegia	↑	◎	160/ 80	bloody	11,600	○	
			2nd attack on hospital day	8h.	dist. of consciousness → coma (3h.)	coma	mydriasis absent	tetraplegia		◎	192/130			○	
13	60	M	3.5h.	25h.	suddenly onset of unconsciousness (coma)	coma	normal size absent	tetraplegia		◎	240/ 130	bloody		○	
14	44	M	6.5h.	19.5h.	headache → lt.hemiplegia, vomiting, dist. of consciousness, dysarthria, rt.lagophtalmus → coma (7h.)	coma	pinpoint present	tetraplegia		◎	200/ 110	bloody	9,200	○	continuous ventricular drainage (1[illegible]h.)
15	33	M	40m.	6h.	headache → coma (1 2h.)	coma	anisocoria present	tetraplegia			170		21,600	○	

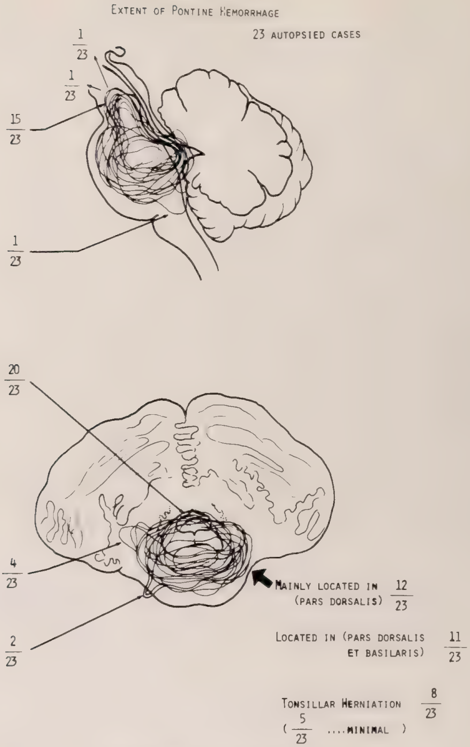
EXTENT OF PONTINE HEMORRHAGE
23 AUTOPSIED CASES
1/23
1/23
15/23
1/23
20/23
4/23
2/23
MAINLY LOCATED IN (PARS DORSALIS) 12/23
LOCATED IN (PARS DORSALIS ET BASILARIS) 11/23
TONSILLAR HERNIATION 8/23
(5/23 ....MINIMAL)

FIG. 1. Extent of pontine hemorrhage.

upward extension of the hematoma into the tegmentum of the midbrain was seen in 15 cases with further extension into the basal ganglia or hypothalamus, each in one case.

The downward extension of the hematoma into the medulla oblongata was seen only in one case. The extension of the hematoma into a brachium pontis was seen in 4 cases. Rupture laterally into the pontine cistern was seen in one case.

Four out of a total of 23 cases had exceptionally long survival of more than 30 days (Case 4, 8, 11, 12) (Fig. 4). The macroscopic findings of these cases varied; Case 8 (34 days survival) showed a massive hematoma which was still

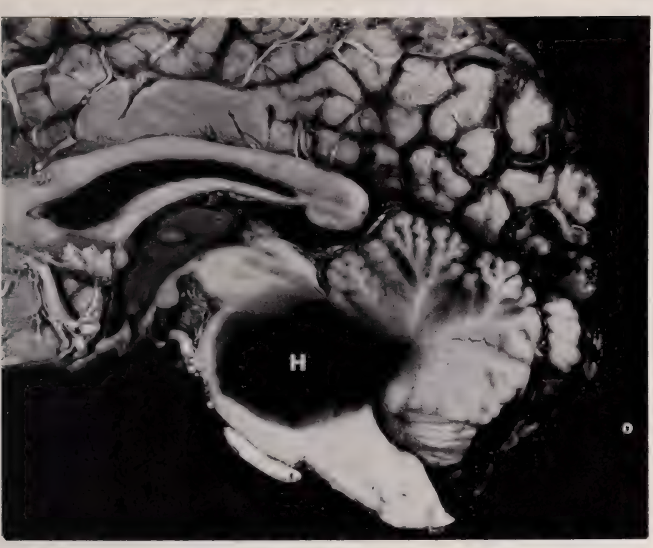

FIG. 2. Autopsy specimen. Case 16 (#17-74). Mid-sagittal section. The hematoma centered in the region of the midpons is seen (H). The hematoma extends into the fourth ventricle and completely fills it with a blood-cast.

of gelatinous consistency; Case 4 (53 days) demonstrated a brownish hematoma with macroscopic capsule surrounding the hematoma and Case 11 (one year and 3 months) showed the scar of an old healed hematoma. Case 12, which clinically had 2 episodes of pontine hemorrhage 2 years and 78 days apart, showed rather complicated pathologic findings. There was a slit-like cyst from the old hematoma on the left side of the basis pontis representing the first episode of hemorrhage and a recent fresh massive hematoma centered in the tegmentum, with rupture into the fourth ventricle which coincided with the second clinical episode. The tonsils were herniated in 8 cases, mild in 5 and moderate to severe in 3. All of these cases showed moderate to severe atherosclerosis of the cerebral vessels.

Injection study: Vascular opacification, interruption and displacement as well as periarterial pooling of the contrast media in the territories of median or paramedian pontine branches which originate from the posterior part of the basilar artery and circumferential pontine arteries, are shown in Table III (in this report, the anatomical nomenclature of the pontine arteries is based upon the classification by Dr. Hassler [4]).

Sudden vascular interruptions were usually encountered in the territories of the median or paramedian pontine arteries. Vascular interruption was also

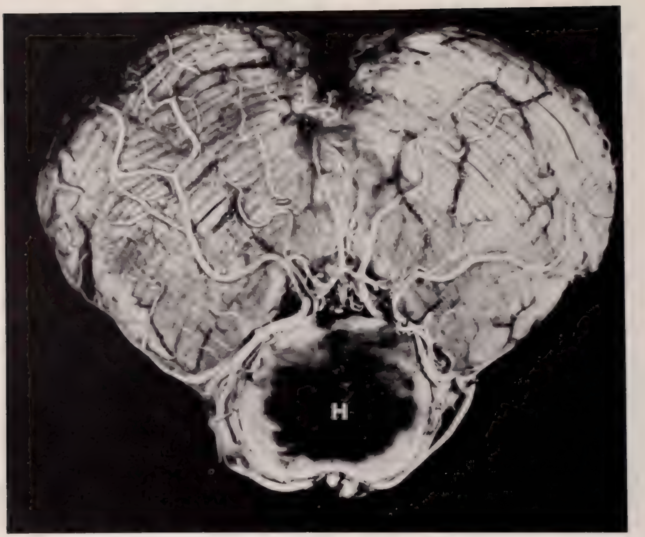

FIG. 3. Case 21 (≠13-75). Autopsy specimen. Horizontal section. The hematoma spreads symmetrically and it involves the entire pons.

seen in the territory of the perforating branch of the most proximal portion of the circumferential pontine artery either alone or in conjunction with the above-described arteries. Centrifugal extension of the hematoma in the midpons displaced the above-mentioned arteries anterolaterally, and the perforating branches of diatal circumferential pontine arteries posterolaterally. Even after careful inspection of injected specimens, it is difficult to ascertain whether the sudden interruption of the pontine arteries was secondary to pressure from the massive hematoma or primary cause of the hematoma. It was also difficult to differentiate periarterial pooling of radiopaque material from spontaneously occurring periarterial microaneurysmal dilatation present in the hematoma or its vicinity. However, these findings were observed most frequently in the territories of median or paramedian pontine arteries and the perforating branches of the circumferential pontine arteries (Fig. 5).

Vertebral angiography: The main angiographic features are summarized in Fig. 6.

Arterial Phase (Fig. 7A, B, Fig. 8A): All of the 23 cases showed moderate to severe arteriosclerosis in the vertebrobasilar system. In the arterial phase of the lateral projection, the basilar artery was displaced toward the clivus in 13 cases. However, stretching of the artery was not definitely identified due to

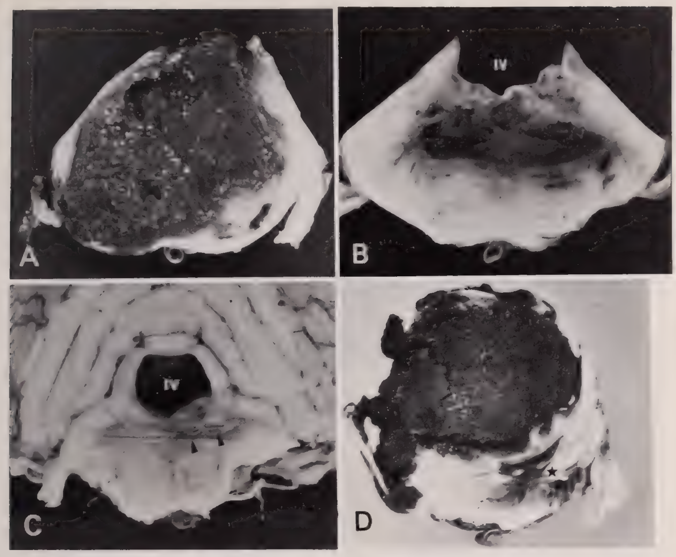

FIG. 4. Autopsy specimens of long-survival cases. Horizontal section.

(A) Case 8 (#30-71). 34 days' survival. Massive hematoma with decreased, gelatinous consistency is noted.

(B) Case 4 (#12-70). 53 days' survival. Brownish old hematoma with macroscopic capsule surrounding the hematoma is noted. The fourth ventricle (IV) is dilated.

(C) Case 11 (#E2-72). 1 year and 3 months' survival. Scar of old-healed hematoma is noted (two arrowheads). The entire pons is atrophic and the fourth ventricle (IV) is dilated.

(D) Case 11 (#28-73). 2 years and 78 days survival after the first episode. Slit-like scar of hematoma in basis pontis on the left side (★) representing the first episode of hemorrhage, and recent massive hematoma centered in the tegmentum with rupture into the fourth ventricle.

increased tortuosity by arteriosclerotic change. The precentral cerebellar branch of the superior cerebellar artery, running in the precentral cerebellar fissure, was displaced backward in 4 cases. Definite elevation and stretching of the anterior culminate and superior vermian segments of the superior cerebellar artery were confirmed in 12 cases, in which the fourth ventricle was found to be enlarged due to intraventricular hematoma. The thalamoperforating arteries arising from the upper end of the basilar artery were usually poorly opacified and, only in 2 cases, were these arteries definitely displaced forward in an arcuate fashion.

In the Towne projection, the circum-mesencephalic portion of the posterior cerebral arteries and lateral pontine segments of the superior cerebellar arteries were stretched and symmetrically laterally displaced in 13 cases.

No definite abnormalities were seen in the course of the anterior inferior

TABLE III

Findings of Pontine Arteries in Injected Specimens (11 cases)

Case	Autopsy no.	Median or paramedian pontine arteries				Circumferential pontine arteries			
		Opacification	Sudden interruption in hematoma and/or its vicinity	Anterolatral displacement	Periarterial pooling of contrast medium	Opacification	Sudden interruption in hematoma and/or its vicinity	Posterolatral displacement	Periarterial pooling of contrast medium
10	28-72	good	+	+	+	good	+	+	+
14	52-73	good	+	+	+	good	±	±	+
15	12-74	fair	+	+	+	fair	+	+	+
16	17-74	good	+	+	±	good	+	+	±
17	28-74	good	+	+	+	good	+	+	+
18	31-74	fair	+	+	+	fair	+		+
19	46-74	fair	+	+	+	fair	+	+	+
20	3-75	fair	+	+	Undetermined (*)	fair	+	+	Undetermined (*)
21	13-75	good	+	±	+	good	+	±	+
22	35-75	fair	+	+	Undetermined	fair	+	+	Undetermined (*)
23	8-76	good	+	+	Undetermined	good	+	+	Undetermined (*)

* Due to excesive leakage of contrast medium.

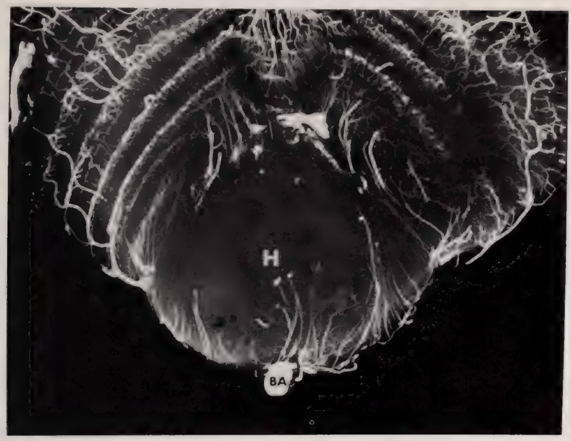

FIG. 5. Injected specimen. Case 10 (#28-72). Sudden vascular interruptions are seen in the territories of the median and paramedian pontine arteries and perforating branches of the proximal circumferential pontine arteries with periarterial microaneurysmal pooling and/or leakage of contrast medium.
H: hematoma. BA: basilar artery.

cerebellar arteries. The lateral and posterior medullary segments of the posterior inferior cerebellar artery were displaced downward to varying degrees in 8 cases with accompanying tonsillar herniation.

The choroidal branches of the posterior inferior cerebellar arteries were not clearly identified in any of the cases. The pontine arteries also were not identified in either conventional vertebral angiograms or angiotomograms.

Venous Phase (Figs. 7C-D, 8B): In the lateral projection, the pontine segment of the anterior ponto-mesencephalic vein (5) was displaced toward the clivus in 13 cases. In 7 of these cases, the hematoma extended into the midbrain resulting in upward and forward displacement of the interpeduncular segment of the vein.

The precentral cerebellar vein (5) running in the precentral cerebellar fissure and, to a lesser extent, the preculminate vein running in the preculminate fissure were displaced posteriorly in 15 and 12 cases respectively. Elevation and stretching of the posterior mesencephalic vein (5) were seen on both sides in 3 cases. In 2 of the three cases, the lateral mesencephalic vein was also stretched and displaced—anterolaterally in one and posterolaterally in the other. The inferior vermian veins (5) were normal in position. In the Town projection, the posterior mesencephalic vein was symmetrically displaced laterally in 12 cases. The transverse pontine vein was not clearly identified due to poor opacification.

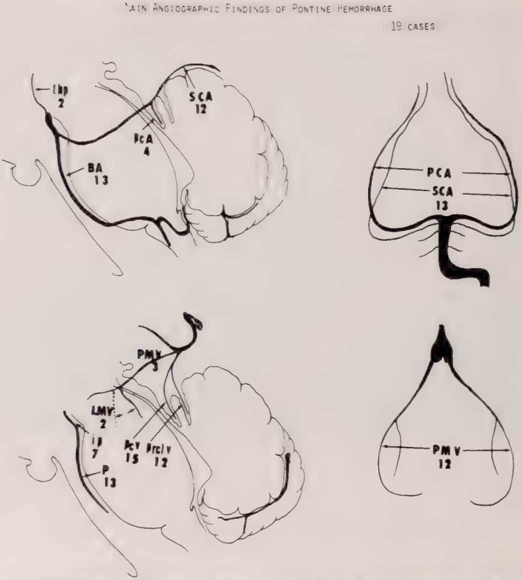

FIG 6. Main angiographic findings of pontine hemorrhage. In the arterial phase, lateral view, the basilar artery (BA) is displaced forward (13/19), precentral cerebellar artery (PcA) backward (4/19), the vermian segment of the superior cerebellar artery (SCA) upward (12/19) and the thalamo-perforating arteries (thp) upward (2/19). In the semiaxial view, the posterior cerebral arteries (PCA) and superior cerebellar arteries (SCA) are displaced laterally (13/19).

In the venous phase, lateral view, the pontine (P) and interpenduncular (ip) segment of the anterior ponto-mesencephalic veins are displaced forward (13/19 and 7/19 respectively). The precentral cerebellar vein (PcV), to a lesser extent, the preculminate veins (prcl V), are displaced backward (15/19 and 12/19 respectively). The posterior mesencephalic veins (PMV) are elevated (3/19). The lateral mesencephalic vein (LMV) may be displaced anteriorly (1/19) or posteriorly (1/19).

In the Towne projection, the posterior mesencephalic veins (PMV) are laterally displaced and separated from each other (12/19).

Angiotomography: The main vessels outlining the median and paramedian posterior fossa structures were clearly visualized by angiotomography using a multisection cassette with 5 mm spacing (Fig. 9). Clearly demonstrated by this technique were displacements and deformities of the precentral cerebellar artery and vein, the anterior ponto-mesencephalic vein and the preculminate vein.

Computerized axial tomography: Hematomas of the pons were shown as a relatively well-demarcated area of high attenuation coefficient. The hematoma which ruptured into the fourth ventricle resulted in enlargement of the latter. Decreased attenuation coefficient around the enlarged fourth ventricle indicated surrounding edema (Fig. 10). In some cases, hematoma extended through both foramina of Monro.

Comment

Varying degrees of atherosclerosis of the major cerebral vessels were noted in all cases. The walls of the pontine arteries were altered diffusely or locally and were irregular in most cases. Our findings suggest that primary pontine hemorrhage, like hypertensive intracerebral hemorrhage elsewhere, is a terminal manifestation in patients with severe hypertensive cardiovascular disease. As seen from the microangiographic studies, the main sites of hematomas are located within the mid-pons. This suggests that the median or paramedian pontine arteries and the perforating branches of the circumferential pontine arteries are the most important vessels in the pathogenesis of pontine hemorrhage as reported by others (1, 9, 10). This anatomical observation, with associated periarterial pooling of contrast media, indicates decreased resistance of the walls of these arteries.

Moscow and Margolis (6) reported the angiographic features of two cases of primary pontine hemorrhage: namely, stretching and lateral displacement of the ambient and quadrigeminal segments of the superior cerebellar arteries, stretching of the interpeduncular perforating vessels indicating rostral extension of the hematoma, anterior displacement of the basilar artery and anterior ponto-mesencephalic vein, posterior displacement of the precentral cerebellar vein, and no displacements of inferior vermian branches of the posterior inferior cerebellar arteries. All of these findings were identified in our cases. In addition, numerous other findings observed in our series include: stretching and symmetrical lateral displacement of the circum-mesencephalic portions of the posterior cerebral arteries, backward displacement of the precentral cerebellar arteries and to a lesser extent, the preculminate veins, upward displacement of the posterior mesencephalic veins and either anterolateral or posterolateral displacement of the lateral mesencephalic veins.

Morphologically, the degree of displacement of these vessels depends upon the degree of enlargement of the pons. According to Fukasawa's morphometric measurements of the brain using 9 cases in this series (3), the values of the cross-sectional area of the upper pons, 3 mm caudal to the superior pontine sulcus, was greater than the normal range in all cases. The edematous white matter surrounding the fourth ventricle demonstrated by CT scan seems related to bulging of the fourth ventricle secondary to intraventricular rupture of the hematoma. Occasionally, this caused difficulty in differentiating a primary pontine hemorrhage from a primary cerebellar hemorrhage on conventional angiograms. Moreover, angiographic appreciation of these conditions is difficult in some cases. In such cases, angiotomography and/or stereoscopic magnification angiography of the posterior fossa were quite useful in delineation of the vessels running in the median and paramedian planes of the posterior fossa. An acute hematoma presented no difficulty in localization by CT Scan.

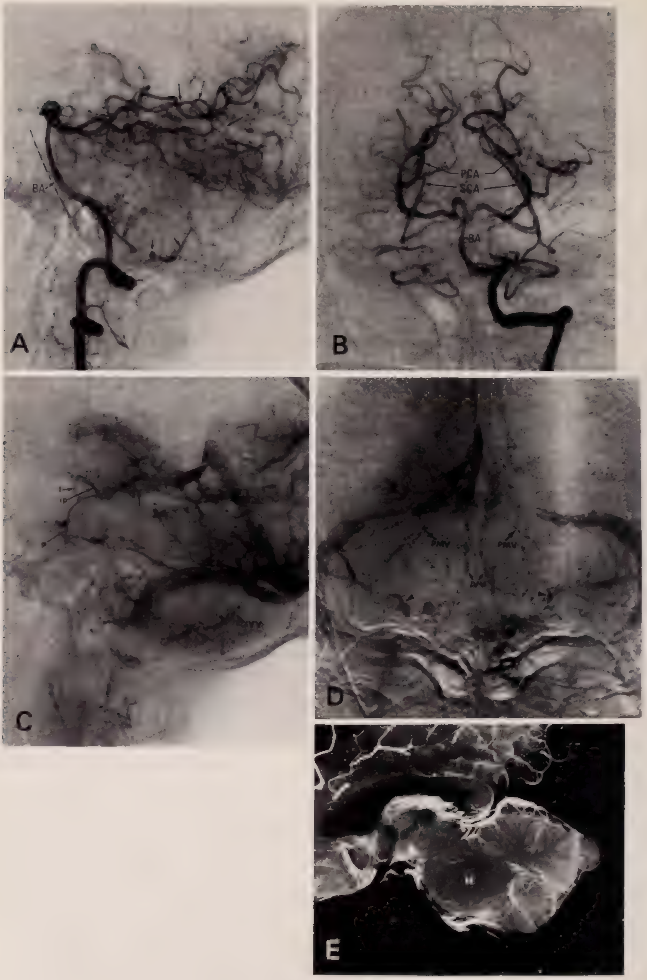
A
BA
B
PCA
SCA
BA
C
D
PMV
PMV
E

FIG. 7. A–E.

Summary

1) A review of twenty-three autopsied cases of primary pontine hemorrhage are presented and their microangiography, vertebral angiography and computerized tomographic findings (one case) are analyzed. Neurological and clinical manifestations on admission are summarized.

2) The hematomas were mainly localized to the midpons; twelve of 23 cases involved the tegmentum pontis and 11 almost the entire pons. Rupture into the fourth ventricle occurred in 20 cases. Upward extension into the tegmentum of the midbrain was seen in 15 cases, whereas downward extension into the medulla oblongata in only one.

3) In injected specimens, the findings of abrupt vascular interruption, displacement and periarterial pooling of the contrast medium were observed mainly in the territories of the median or paramedian pontine branches and/or the perforating branches of the most proximal circumferential pontine arteries. This suggests decreased resistance in the walls of these arteries.

4) On vertebral angiograms, the vessels running in median and paramedian planes of the posterior fossa were displaced posterolaterally by the hematoma of the pons. These findings were well demonstrated by the angiotomographic technique. Also the location of the hematoma and the edema surrounding the enlarged fourth ventricle in the acute state were clearly visualized by computerized tomography.

5) The neurologic and clinical manifestations on admission of abrupt onset of coma, miotic pupil or anisocoria, quadriplegia, hyperthermia, bloody CSF and preexisting hypertension were seen in almost all cases. There was in four cases an exceptionally long survival of more than 34 days attributed to adequate control of respiration.

FIG. 7. Case 16 (same case as Fig. 2). A 54 year-old male. Left vertebral angiogram.

(A) Arterial phase in lateral projection. The basilar artery (BA) is stretched and displaced toward the clivus (dashed line). The anterior culminate and superior vermian segments of the superior cerebellar arteries are stretched and elevated (large arrows). The proximal somewhat tortuous posterior inferior cerebellar artery on the left side is stretched and displaced downward (small arrows).

(B) Arterial phase in Towne projection. The lateral pontine segments of the superior cerebellar arteries (SCA) and the circum-mesencephalic segments of posterior cerebral arteries (PCA) are stretched and symmetrically laterally displaced. The basilar artery (BA) is also stretched. Moderate arteriosclerotic changes of the vertebro-basilar system are seen.

(C) Venous phase in lateral projection. The pontine segment of the anterior ponto-mesencephalic vein (P) is stretched, whereas the interpeduncular segment (ip) and lateral anterior ponto-mesencephalic vein (1) are normal in location. The colliculo-central point (o) of the precentral cerebellar vein (arrowheads) is displaced upward and somewhat backward. The posterior mesencephalic veins (arrows) are stretched and elevated on both sides. The copular point (large arrowhead) of the inferior vermian vein (IVV) is normally located and the anteroposterior diameter of the medulla oblongata (♂♂) is unremarkable.

(D) Venous phase in the Towne projection. The posterior mesencephalic veins (PMV) are symmetrically superolaterally displaced. No abnormalities are seen in the course of the petrosal veins (large arrowheads), the vein of the lateral recess on the left (small arrowheads) or the inferior vermian veins (IVV).

(E) Same case. Injected specimen. Mid-sagittal section. The pontine arteries surrounding the hematoma are stretched and displaced superiorly or inferiorly. The precentral cerebellar arteries running in the precentral cerebellar fissure and the twigs originating from anterior culminate segment of the superior cerebellar artery running in the preculminate fissure are displaced backward and upward.

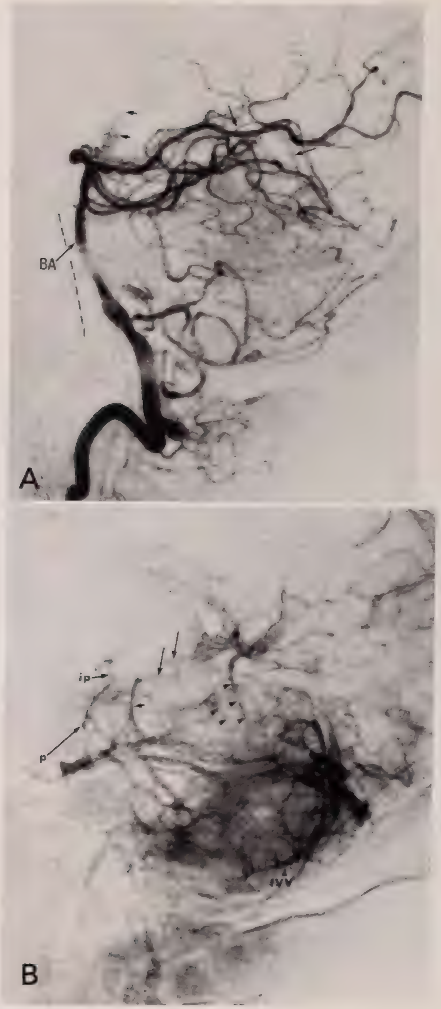
BA
A
ip
p
IVV
B

FIG. 8. A–B.

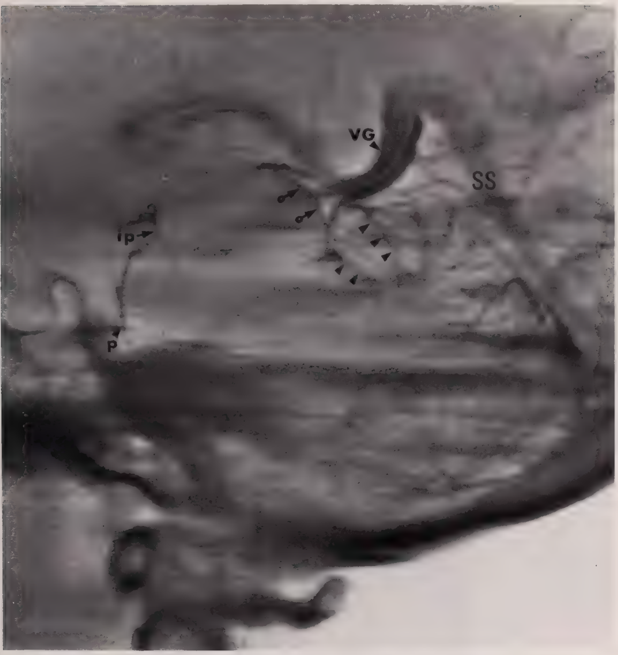

FIG. 9. Case 10 (same case as Fig. 5). A 55-year-old male. Angiotomogram. Venous phase, lateral view. The interpeduncular (ip) and pontine segments of the anterior ponto-mesencephalic vein are stretched and displaced anterosuperiorly, whereas the longitudinally running tectal vein (♂) which demonstrate the posterior border of the tectum is displaced posteriorly indicating the increased anteroposterior diameter of midbrain. The pontine segment (P) of the anterior ponto-mesencephalic vein is displaced anteriorly toward the clivus and stretched. The precentral cerebellar (2 arrowheads) and preculminate veins (3 arrowheads) are displaced backward and upward. The straight sinus (SS) and vein of Galen (VG) are also labeled.

FIG. 8. Case 18. A 59-year-old male. Left vertebral angiogram.

(A) Arterial phase, lateral view. The basilar artery (BA) is somewhat compressed against the clivus (dashed line) and the thalamoperforating arteries originating from the upper end of the basilar artery are stretched and straightened (small arrows). The vermian segments of the superior cerebellar arteries are stretched and elevated (large arrows).

(B) Venous Phase, lateral view. The upper portion of pontine (P) and interpeduncular (ip) segments of the anterior ponto-mesencephalic vein are stretched and displaced anterosuperiorly. The lateral mesencephalic vein is displaced anteriorly and stretched (small arrow). The posterior mesencephalic veins (large arrow) are narrow, stretched and anteriorly displaced. The first segment of the faintly visualized precentral cerebellar vein (2 arrowheads) and the preculminate vein (3 arrowheads) are displaced backward and upward. The inferior vermian vein (IVV) is normal in location.

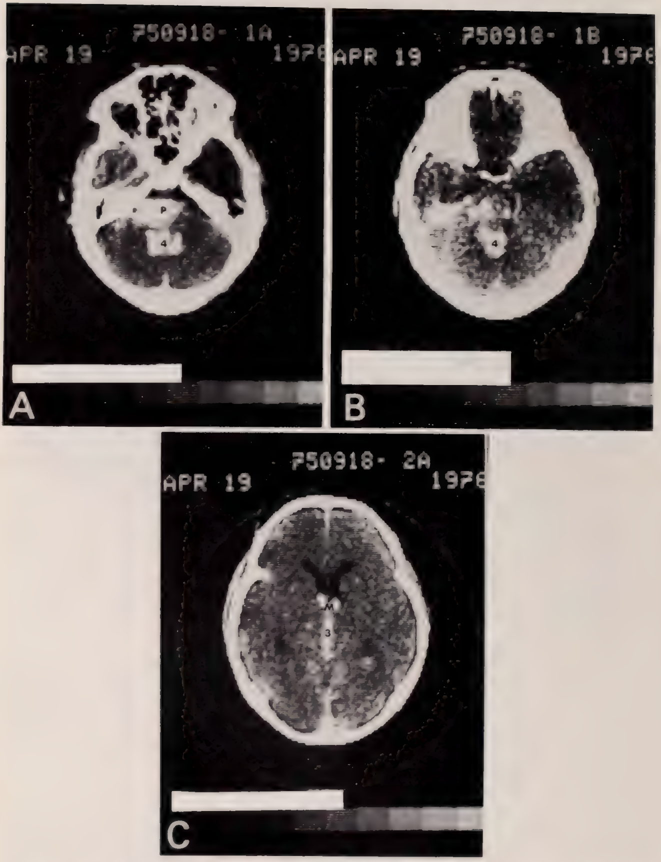
750918- 1A
APR 19
197
P
4
A
750918- 1B
APR 19
197
4
B
750918- 2A
APR 19
197
M
3
C

FIG. 10. Case 23. A 45-year-old male. Computerized tomogram. Serial 8 mm thick CT scans as reviewed from below upward.

(A) A demarcated hematoma involving almost the entire pons (P) is seen. The hematoma extends into the fourth ventricle (4) which is enlarged and filled with a blood-cast.

(B) An area of low attenuation coefficient surrounding the enlarged fourth ventricle (4) indicates the presence of edema.

(C) The hematoma also fills the third ventricle (3) and both foramina of Monro (M).

Acknowledgment

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Perforated Leiomyosarcoma of Meckel's Diverticulum: A Case Report and Review of Literature

MAHENDRA SHETH, M.D., VLADIMIRO ROSENBERG, M.D., AND UNSUP KIM, M.D.

Abstract

Malignant tumors of Meckel's diverticulum are rare. Leiomyosarcoma is the most frequently encountered sarcoma in this location. Tumors can acquire a great size and outgrow their blood supply, resulting in necrosis and perforation. A case of perforated leiomyosarcoma of Meckel's diverticulum is described. Review of the literature reveals 50 reported cases.

Primary malignant neoplasms of Meckel's diverticulum are uncommon. Carcinoids, adenocarcinoma, and sarcomas of variable histology have been described. Leiomyosarcoma is the most frequently encountered sarcoma. A case of perforated leiomyosarcoma, that presented as acute abdomen, is reported along with a review of recent literature.

Case Report

A 45-year-old caucasian male patient was admitted to the Mount Sinai Services, City Hospital Center at Elmhurst, complaining of increasing abdominal pain of six hours duration, associated with nausea and vomiting. Pain started around the mid-abdomen and quickly became generalized. Patient was always in good health, except for an episode of epigastric pain, nausea and vomiting one week prior to admission and lasting for about 8–10 hours. There was no history of weight loss, anorexia, change in bowel habits, or bleeding per rectum.

Physical examination on admission disclosed rectal temperature of 102.8°F., pulse rate of 120/minute, and blood pressure of 130/80 mm. of Hg. Patient appeared in acute distress. Abdominal examination revealed moderate distension of the abdomen with generalized rigidity and diffuse tenderness. There were no palpable masses and bowel sounds were absent. On rectal examination there was bilateral pelvic tenderness, there were no palpable masses and stool guaiac was negative.

Laboratory findings showed a hemoglobin of 12.6 gms.%, WBC of 14,000/c.m.m. with marked shift to the left. Serum electrolytes, blood urea nitrogen, blood sugar, and serum amylase were within normal range. Chest x-ray was normal. Flat and upright film of abdomen revealed a large mass density in mid and lower abdomen with an air fluid level (Fig. 1–2).

Nasogastric decompression, intravenous fluids, and systemic antibiotics were instituted, and emergency exploratory laparotomy was performed. Peritoneal cavity contained 1500 cc. of cloudy blood stained fluid. A large mass measuring 20 × 13 × 8 cm. was found arising from the small bowel about 80 cms. from the ileocecal valve (Figure 3). There was a large cavity within the mass which was communicating with the lumen of the small intestine and had perforated into free peritoneal cavity (Figure 4–5). The liver was found to be free of any palpable lesions. Resection of tumor with adjacent intestine was done. The peritoneal cavity was irrigated with normal saline and pelvis was drained using sump and penrose drains. Postoperative course was uneventful. Patient is asymptomatic and free of detectable lesion two years after resection.

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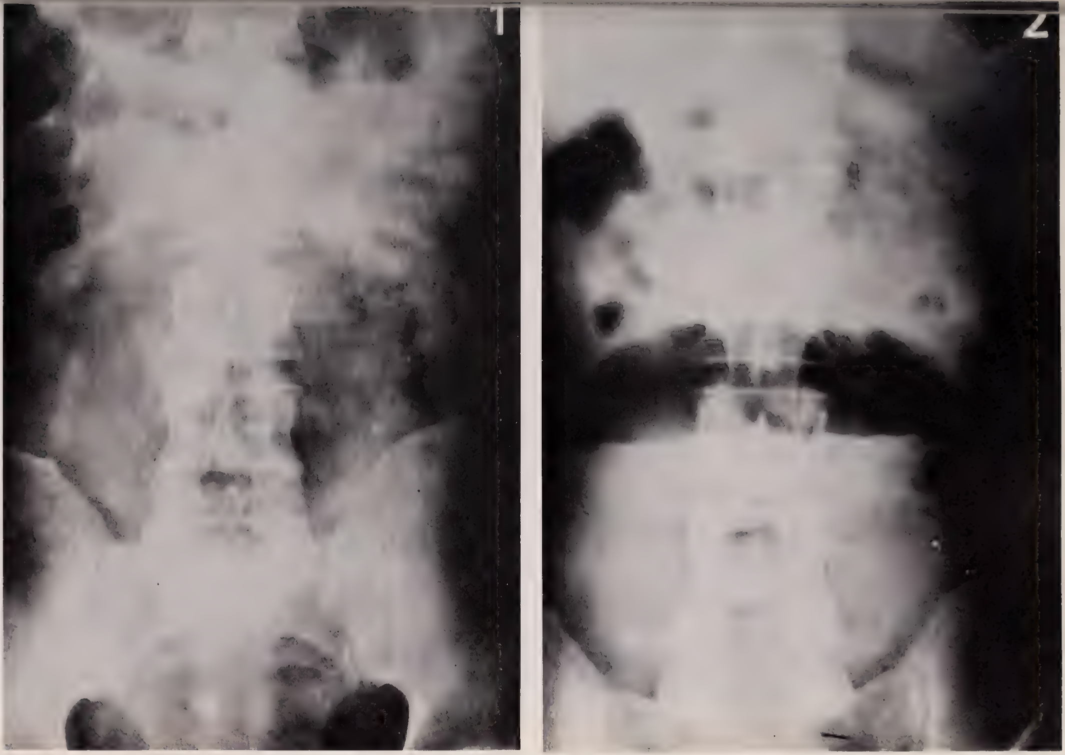


FIGS. 1 and 2. Flat and upright x-rays of abdomen showing large soft tissue density with air fluid level.

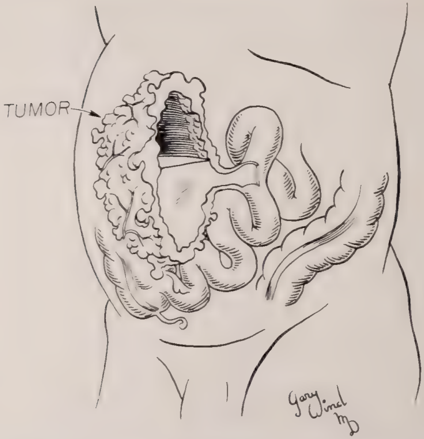


FIG. 3. Schematic presentation of operative findings showing large tumor mass with cavitation.

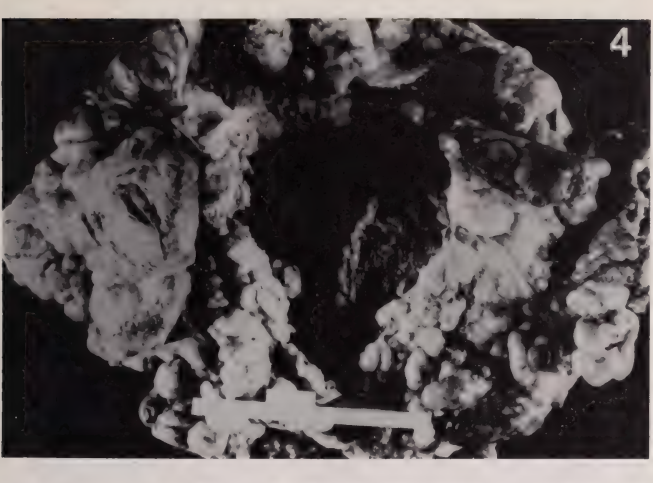
Pathology findings: Specimen was a cystic mass measuring 20 × 13 × 8 cm. and weighing 1300 grams. External surface of the mass showed nodular appearance with yellowish white discoloration. Wall of the mass measured 0.5 cm. to 3 cm. in thickness. Inner surface of the wall was coated with brownish necrotic tissue. Cut surface of the nodules showed yellowish white homogenous elastic soft tumor tissue.

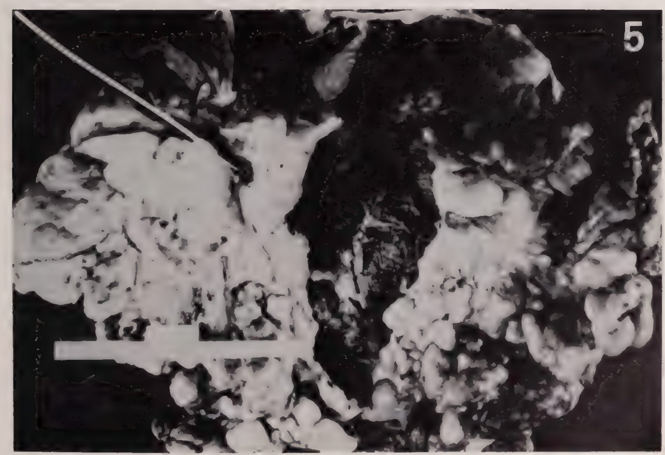
Microscopic examination showed spindle shaped cells with areas of cellular and nuclear pleomorphism and mitosis. Multinucleated tumor giant cells were also present (Figure 6–7). Tumor tissue extends from submucosa of small intestine into muscular layers. Resection margins were covered with normal mucosal cells. There was no vascular invasion noted.

Discussion

Sarcomas of Meckel's diverticulum are rare tumors. In review of literature in 1963, Weinstein, Dockerty, and Waugh (1) were able to collect 35 cases. The accumulated series consisted of 17 leiomyosarcomas, 12 spindle cell sarcomas, 3 lymphosarcomas, 2 fibrosarcomas, and 1 sarcoma of undifferentiated type. Haugen, Pegg, and Kyle (2, 3) in 1970 updated the total number to 44. Six additional cases have been reported in recent literature bringing the total number of reported cases to 50 (4, 5, 6, 7). Reticulum cell sarcoma has never been reported even though it is the most common malignant neoplasm of small intestine (2).

Leiomyosarcoma in Meckel's diverticulum appears to develop in patients above age 20. In series reported by Weinstein et al, age ranged from 22 to 76 with mean of 51 years. Both sexes are affected equally. Most frequent symptoms associated with this disease are abdominal pain with nausea, vomiting, and melena. Other symptoms in decreasing order of frequency are fever,





FIGS. 4 and 5. Gross operative specimen, 20 × 13 × 8 cms. in size, showing nodularity, large cavity, and perforation indicated with a metal probe.

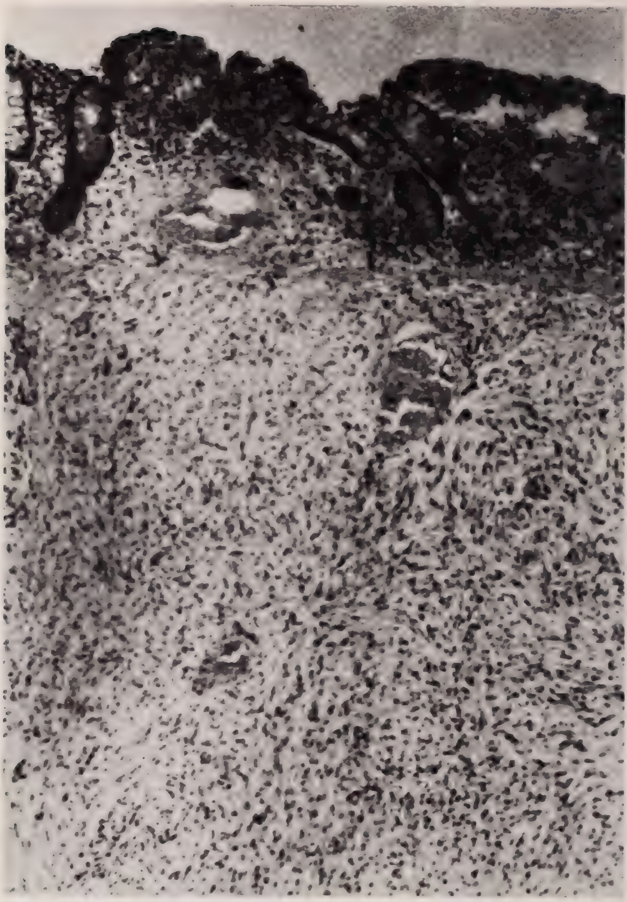


FIG. 6. Microscopic specimen in low magnification.

abdominal fullness, loss of weight, abdominal mass, and diarrhea. Intestinal obstruction is rare. One of two cases, reported by Tzaneu and Popdimitrou, perforated causing acute abdomen (1).

Tumors vary in size a great deal from 1-2 cm. in diameter to 20 cm. in

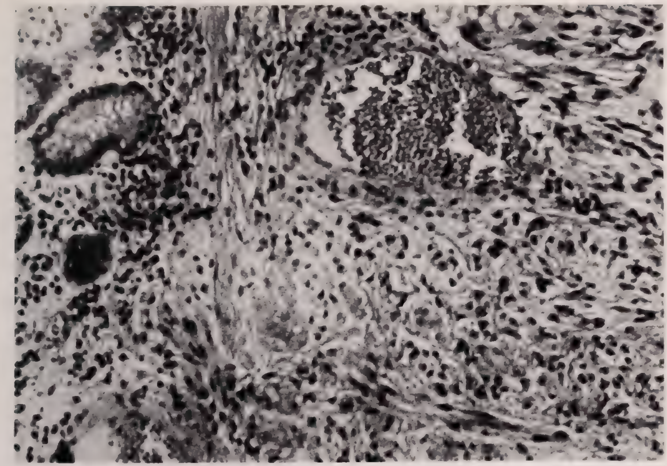


FIG. 7. Microscopic specimen in high magnification showing spindle shaped cells with areas of cellular and nuclear pleomorphism and mitoses. Some multinucleated giant cells are also present.

diameter as reported in this case. In cases of large tumors, it may be difficult to identify any uninvolved part of Meckel's diverticulum.

In such cases, location of tumor in relation to ileocecal valve and enlarged remnants of the vitelline vessels is important (1, 8). The remnant consists of an artery and a vein that arise from the mesentery of the ileum and cross the intestine to supply the tumor. These vessels are normally small but with enlarging tumor they become extremely large. Large tumors may outgrow their blood supply causing necrosis, cavitation, hemorrhage, and perforation.

Frequently, it is difficult to decide whether a given tumor is benign or malignant on histologic examination since sarcomas bear a similarity to leiomyomas. According to reports by Golden and Stout (9) and Starr (10), cellularity with pleomorphism in given tumor with two or more mitoses per high power field one can be certain in predicting malignancy. Most leiomyosarcomas are slow growing tumors. About one-quarter of documented cases metastisize either by direct invasion of neighboring organs, peritoneal implant, or vascular embolization. Lymphatic spread is infrequent.

Resection of lesion along with ileum affords best results. Adjuvant chemotherapy may improve results in selected cases. Published follow-up series are not available to comment on long term prognosis.

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Conservative Management of Life-Threatening Hemoptysis

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Abstract

Twenty patients with hemoptysis of more than 200 ml in 24 hours are reported. All were initially treated medically. Recovery occurred in 14 patients with continued conservative management and in three treated surgically. Two patients with inoperable carcinoma of the lung and one with bilateral active tuberculosis and poor pulmonary function died, two within minutes of the onset of bleeding.

We conclude that most patients with life-threatening hemoptysis can be managed conservatively regardless of the amount of bleeding in the first 24 hours or the presence of aspiration of blood. We recommend surgery for operable patients when hemoptysis of 200 ml recurs after previous bleeding has stopped, if there is difficulty maintaining a patent airway because of very rapid bleeding, or when shock is present.

Occasionally hemoptysis is so voluminous or brisk that a patient's life is threatened. Several studies have advocated emergency surgery in management of massive or significant hemoptysis (1–6).

In this report we review our experience with life-threatening hemoptysis in 20 patients, emphasize conservative management of this problem, and present our indications for surgical intervention.

Methods

From July 1964 to March 1976, 20 patients with hemoptysis greater than 200 ml in 24 hours were evaluated on the medical service of the Mount Sinai Services-City Hospital Center at Elmhurst.

All patients had frequent hematologic studies, daily chest roentgenograms, and several sputum smears and cultures for routine bacteria, mycobacteria, and fungi. Thoracic surgical consultation was obtained and bronchoscopy was performed as soon as possible after admission to the hospital. Rigid bronchoscopy was initially performed from 1964 to 1973 and fiberoptic bronchoscopy from 1973 to 1976. Both procedures were utilized on two patients.

Results

Age and sex of the 20 patients with life-threatening hemoptysis, diagnosis, volume of blood, duration of bleeding, history of previous hemoptysis, presence or absence of aspiration, and outcome are shown in Table I.

Table II summarizes the number of patients and outcome by diagnosis. In

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TABLE I

Clinical Features in 20 patients with Life Threatening Hemoptysis

Case no.	Age/Sex	Diagnosis	Volume (ml)	Duration (days)	Previous hemoptysis	Aspiration	Outcome
1	24/M	Active Tuberculosis	600/16 hrs	4	No	No	Recovery
2	22/M	Active Tuberculosis	500/10 min	3	Yes	?	Fatal hemoptysis from other lung 3 weeks later
3	20/F	Active Tuberculosis	300/24 hrs	3	No	Yes	Recovery
4	35/M	Active Tuberculosis	700/24 hrs	3	Yes	?	Recovery
5	23/M	Active Tuberculosis	600/24 hrs	10	No	Yes	Recovery
6	75/M	Inactive Tuberculosis	500/24 hrs	5	Yes	Yes	Recovery
7	61/M	Inactive Tuberculosis	200/24 hrs	6	Yes	No	Recovery
8	24/M	Inactive Tuberculosis	600/4 hrs	3	No	No	Recovery
9	39/F	Inactive Tuberculosis	600/10 hrs	recurrent 200/24 hrs	No	Yes	Surgery Recovery
10	66/M	Inactive Tuberculosis	200/24 hrs	recurrent 600/24 hrs	Yes	No	Surgery Recovery
11	48/M	Carcinoma	1000/5 min		No	?	Died
12	67/M	Carcinoma	500/24 hrs	2	No	Yes	Recovery
13	44/F	Carcinoma	600/24 hrs	recurrent fatal	No	Yes	Fatal hemoptysis after recurrent bleeding
14	71/F	Bronchiectasis	400/24 hrs	2	No	Yes	Recovery
15	36/M	Bronchiectasis	250/24 hrs	3	Yes	No	Recovery
16	69/M	Bronchiectasis	300/24 hrs	2	Yes	No	Recovery
17	45/F	Mitral Stenosis	500/12 hrs	2	Yes	Yes	Recovery
18	55/M	Aspergilloma	400/24 hrs	3	No	No	Recovery
19	24/F	Undetermined	300/24 hrs	3	No	Yes	Recovery
20	63/M	Undetermined	600/5 hrs	recurrent 200/24 hrs	No	No	Surgery Recovery
			Average 500/24 hrs	2–6	8 Yes	9 Yes	17 Recovery 3 Died 3 Surgery

two patients the cause of pulmonary hemorrhage could not be determined after extensive investigation including lobectomy in one patient. Operative and postoperative complications occurred in two out of three patients and included cardiac arrest, pneumonia, and empyema.

Mortality in medically and surgically treated patients with life-threatening hemoptysis is shown in Table III. Two of the three fatalities occurred within minutes after the onset of hemoptysis.

Discussion

The major decision in management of patients with hemoptysis is whether to operate or to wait until bleeding stops with specific or nonspecific medical treatment. This problem has been reviewed under the heading of massive hemoptysis (1–5) and significant hemoptysis (6). Patients included in these studies bled 100 to 600 ml or more in 24 to 48 hours. Since patients may suffocate and die from less than massive amounts of blood in the bronchial tree if the bleeding is sufficiently brisk, and since any hemoptysis may indicate a serious underlying disease, we prefer the term life-threatening hemoptysis when either the volume or rapidity of bleeding endangers the life of a patient. The amount of blood measured in the hospital is often only a rough estimate of total bleeding because many patients have bled predominantly prior to admission or have aspirated or swallowed blood. All our patients bled at least 200 ml, with an average of 500 ml in 24 hours. Eight patients bled 600 ml or more.

There were 14 men and six women in our series with an age range from 20 to 75 years. The major cause of hemoptysis was tuberculosis, as seen in 10 patients, five with active and five with inactive disease. Three patients had

TABLE II

Cause and Outcome of Life-Threatening Hemoptysis in 20 Patients

Diagnosis	Number of patients	Outcome	
		Death	Recovery
Tuberculosis	10		
Active	5	1	4
Inactive	5		5
Carcinoma	3	2	1
Bronchiectasis	3		3
Mitral Stenosis	1		1
Aspergilloma	1		1
Not Determined	2		2
Total	20	3	17

TABLE III

Mortality in Life-Threatening Hemoptysis

Mode of treatment	Number of patients	Number of deaths
Medical	17	3 (18%)
Surgical	3	0

carcinoma of the lung, three bronchiectasis, one mitral stenosis, one aspergilloma, and two patients had hemoptysis of undetermined origin. The age distribution, sex ratio, and underlying conditions are similar to those reported previously (1, 2, 4).

The age, volume of blood, history of previous hemoptysis, and occurrence of aspiration of blood did not affect the outcome in our patients. Crocco et al (1) and later Gourin and Garzon (2) recommended surgery for patients with hemoptysis greater than 600 ml in 24 to 48 hours. Amirana et al (6) stressed the importance of the presence or hazard of aspiration in considering patients for surgery. Pursel and Lindskog (7) emphasized inability to maintain an airway because of continuous bleeding and impending shock despite ample support of blood volume.

In most of our patients brisk or voluminous hemoptysis lasted less than 24 hours, occurred in one or two major episodes, and bleeding gradually subsided completely in two to six days. Our major indication for surgery was recurrent bleeding of at least 200 ml, as seen in three patients. We would also operate when there is difficulty maintaining a patent airway because of very rapid bleeding or when shock is present. Two of the three fatalities occurred within minutes after the onset of hemoptysis. Two of these patients had inoperable carcinoma of the lung. The patient with active tuberculosis died three weeks after his first episode of hemoptysis from the right lung with hemorrhage from the left lung and was inoperable because of bilateral disease and poor pulmonary function. Thus none of our patients who died could have been saved by surgery. Yeoh et al (3) reported that eight of 10 patients died within minutes after hemoptysis began. We feel that medical management is particularly preferable in patients with a readily treatable disease such as bacterial infection or active tuberculosis, especially when tuberculosis is bilateral or a pneumonectomy would be required.

Previous authors have reported a mortality of 23 to 75% with conservative treatment of massive pulmonary hemorrhage, and have emphasized the necessity for surgical intervention in operable patients (1–3). Although tuberculosis is the sole or predominant condition causing hemoptysis in most reports, emergency surgery has also been recommended for massive pulmonary hemorrhage in mitral stenosis (8), and lung abscess filled with blood clots (9). Surgical mortality has ranged between 18 and 23% (1, 2, 4). Gourin and Garzon (2) reported a mortality of 8% in patients with bleeding that had stopped at the time of pulmonary resection and where in effect prophylactic surgery was performed. None of our patients treated surgically died. The complication rate after emergency surgery has been high, as seen in our study (2).

We agree with previous authors (1) that surgery should not be considered in patients with bilateral far advanced tuberculosis, poor pulmonary function, inoperable lung cancer, and when the site of bleeding cannot be localized.

Medical treatment with bed rest is given initially to all patients admitted with hemoptysis (1, 3). A patent airway should be maintained and the patient lie with the bleeding site dependent and not be oversedated with codeine or other drugs so as to prevent aspiration to other areas of the lungs. Vital signs, hemoglobin concentration, hematocrit, and chest roentgenograms should be monitored frequently. Coagulation defects should be sought and corrected when found. Occasional patients may require blood transfusions. Antibiotics and antituberculosis drugs should be given when indicated. Although the source of hemorrhage can be identified on chest roentgenograms in most cases, it should be confirmed by bronchoscopy while the patient is actively bleeding as soon as possible after admission to the hospital. Fiberoptic bronchoscopy is now the method of choice (10) unless bleeding is massive, in which case rigid bronchoscopy may be preferred. When hemoptysis recurs bronchoscopy should be repeated in patients with bilateral disease since the new bleeding may be from the opposite side, as seen in one of our patients. The use of vasopressin, conjugated estrogenic substances, vitamin K, and vitamin C is probably ineffective (1). New methods in the management of life-threatening hemoptysis are localization by selective pulmonary angiography (11) and endobronchial tamponade therapy with a Fogarty catheter (12).

It is very difficult to compare the results of different studies. Our data show a better prognosis for conservatively treated patients with life-threatening hemoptysis than reported previously. Although we elected to perform surgery on operable patients with recurrent hemoptysis of 200 ml or more, we do not know that their bleeding would have continued with further conservative treatment. In one patient with bilateral active tuberculosis hemoptysis recurred several times and finally stopped after 10 days.

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Ureteral Obstruction Secondary to Iliac Artery Aneurysms

ARIEH KAYNAN, M.D., VLADIMIRO ROSENBERG, M.D., AND PINKUS SZUCHMACHER, M.D.

Abstract

Iliac artery aneurysms usually remain asymptomatic until progressive enlargement results in rupture or extrinsic displacement and compression of surrounding structures. The majority of the cases are seen initially by a urologist, gynecologist, or an internist, with symptoms referable to the pelvic organs. When obstructive uropathy is caused by an iliac artery aneurysm, the ureter may be encased in dense fibrotic tissue. In such cases only lysis will release the obstruction. On the other hand, if the occlusion is mainly due to compression of the ureter against the pelvic brim, vascular reconstruction alone will alleviate the hydronephrosis. Two cases of hydroureter caused by expanding iliac artery aneurysms are reported. Diagnostic approaches and surgical treatment are discussed, together with follow-up studies of the hydroureters demonstrating marked diminution in their size following surgical corrective procedures.

Introduction

The ureters cross the distal common iliac arteries in their pelvic course. This anatomical arrangement renders them vulnerable to obstruction by enlarging iliac artery aneurysms. Awareness of this anatomical relationship will not only facilitate the preoperative evaluation, but will also lead to a better planning of the corrective surgical procedures.

Two cases of obstructive uropathy secondary to iliac artery aneurysms are reported with particular emphasis on the mode of surgical correction.

Case Reports

Case 1. A 69-year-old white female was admitted to the gynecological ward of Mount Sinai Services-City Hospital Center at Elmhurst on 7/12/76 because of a right pelvic mass which was found during a routine examination. The patient admitted to increasing abdominal girth and frequent micturition. She was a known hypertensive on Methyldopa (Aldomet).

On physical examination, the blood pressure was 160/100 mm Hg pulse 80 per minute and regular, temperature 98°F. The abdomen was soft with no palpable masses. Pelvic and rectal examination revealed a mass in the right lower quadrant. Although the femoral pulses were easily palpable, the distal pulses could not be felt. The x-ray of the chest revealed no evidence of active pulmonary disease. Barium enema was normal and a flat plate of the abdomen showed a calcified rim in the right pelvis. The EKG demonstrated normal sinus rhythm. The urinalysis was within normal limits and the rest of the laboratory findings were unremarkable.

Following a negative dilatation and curettage on 7/22-76, a celiotomy for a right ovarian tumor was performed, at which time a right common iliac and a large right hypogastric artery aneurysm occupying the entire pelvis was found. The abdomen was closed and the patient was transferred to the Vascular Service.

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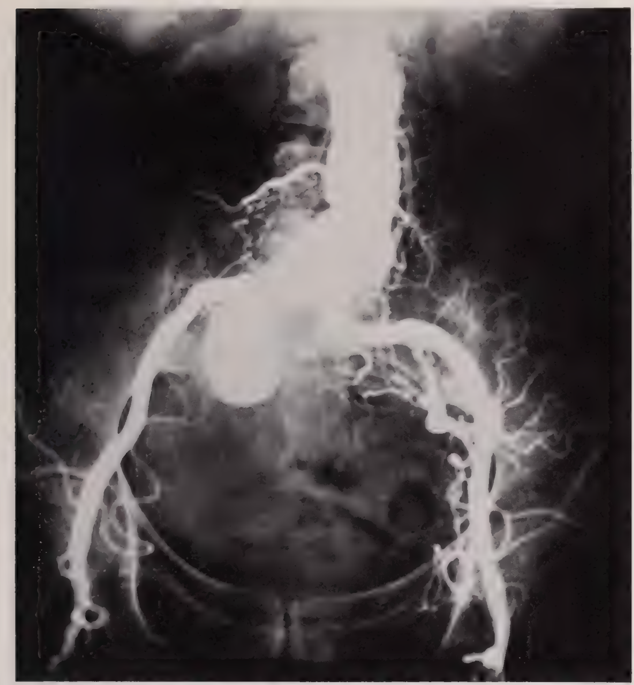

FIG. 1. Translumbar aortogram showing the right common iliac and the large right hypogastric artery aneurysms.

Translumbar aortogram confirmed the operative findings (Fig. 1). It also demonstrated pressure on the bladder by the aneurysm as well as a right hydroureter. Subsequent intravenous pyelography showed hydroureter on the right side (Fig. 2). The left kidney and ureter were normal.

On 8/31/76, through a midline incision, the neck of the hypogastric aneurysm was ligated and the right common iliac aneurysm was excised. Aorto right external, left common iliac bypass was carried out using a #18 bifurcated woven dacron graft. No attempt was made to lyse the ureter. The postoperative course was uneventful.

6 months later, an IVP demonstrated a marked diminution in the size of the right ureter (Fig. 3) and the symptoms of frequent micturition have disappeared.

Case 2. A 34-year-old white male was admitted to St. John's Episcopal Hospital with abdominal pain of 2 days duration associated with nausea and anorexia. The past medical history included drainage of a lesser sac abscess in 1959, treatment for sub-bacterial endocarditis for 3 months and 3 incisional hernioplasties.

Apart from a Grade IV/VI systolic murmur over the precordium and soft, mildy distended abdomen with epigastric tenderness, the pertinent physical findings on admission were normal

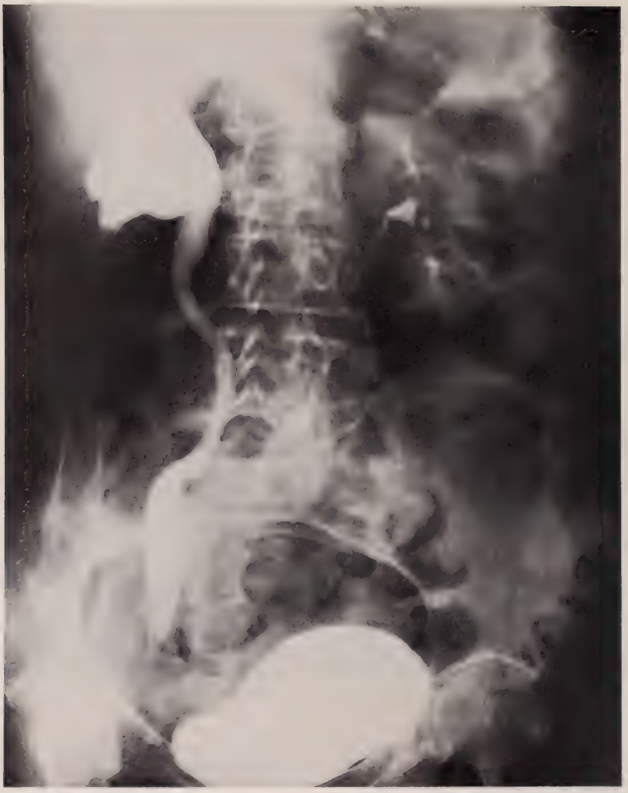

FIG 2. Preoperative I.V.P. demonstrating the bladder displacement, the large right hydroureter and hydronephrosis.

pulses in the right lower extremities, while the left femoral pulse was slightly decreased with good distal pulses. The rectal examination was negative. The blood pressure was 150/70 mm/Hg, pulse 120 per minute, temperature 100°F. Chest x-ray was normal. Abdominal films revealed findings compatible with ileus. Laboratory findings showed a hemoglobin of 12.5 gm. % with a white blood cell count of 8,500/mm^3, normal electrolytes and a serum amylase of 325 international units.

The patient was treated for acute pancreatitis with some improvement; however, he continued to have bouts of crampy abdominal pain, which were relieved by nasogastric intubation. On 4/29/75, the abdomen became markedly distended. X-rays, at this time, revealed a pattern of partial small bowel obstruction which was treated with a long gastrointestinal tube. The white blood count, serum electrolytes and amylase were all normal. His condition did not improve and

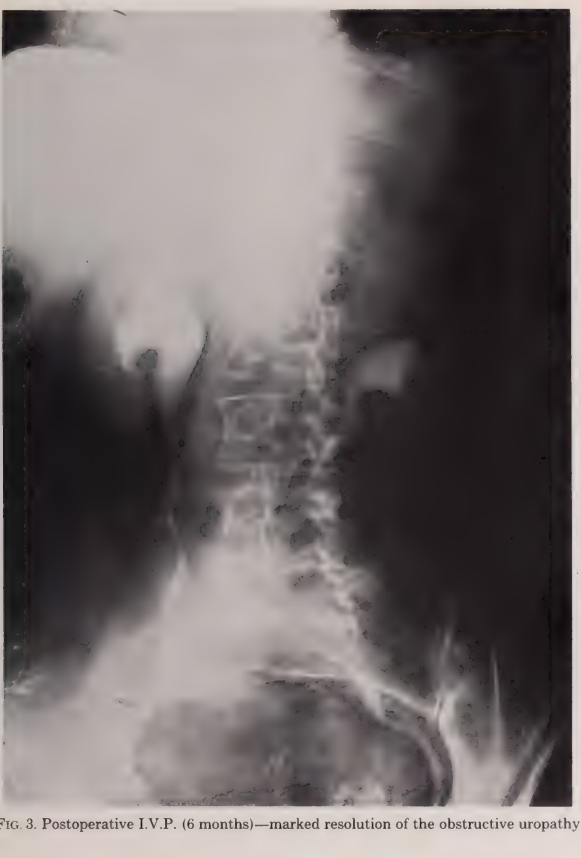

FIG. 3. Postoperative I.V.P. (6 months)—marked resolution of the obstructive uropathy.

on 5/2/75, he underwent a laparotomy and lysis of adhesions to relieve the small bowel obstruction. At this time, a large pulsatile pelvic mass overlying both iliac vessels was found. The abdomen was closed.

Postoperatively, a translumbar aortogram showed occlusion of the left common iliac artery at the level of the aortic bifurcation (Fig. 4). An IVP demonstrated a large left hydroureter (Fig. 5). Multiple blood cultures were negative.

On 5/19/75, the patient was re-explored and endoaneurysmorrhaphy of a right iliac aneurysm occluding the left common iliac artery was performed. The left ureter was dissected free from its thick, fibrous encasement. Culture of the aneurysmal wall was negative.

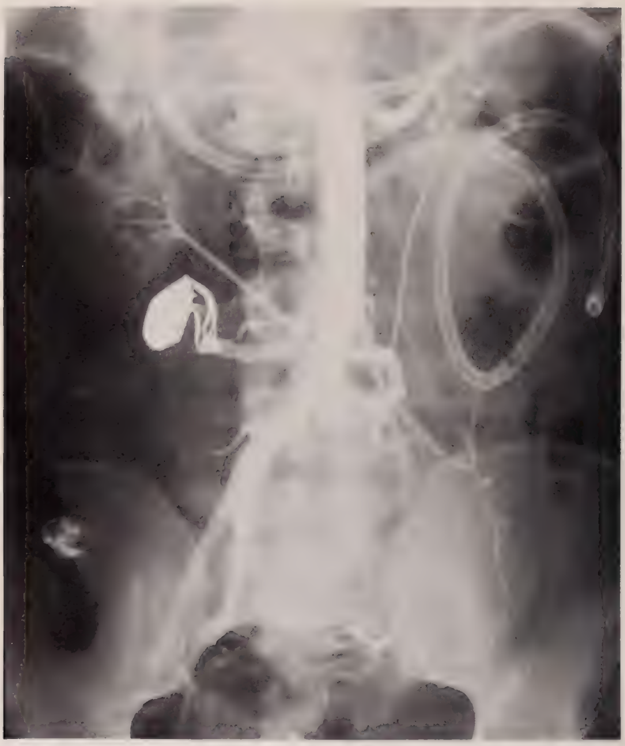

FIG. 4. Translumbar aortogram showing occlusion of the left common iliac artery.

The postoperative course of the patient was uneventful. Repeat IVP in July 1975 revealed a normal renal collecting system and normal size ureter (Fig. 6).

On a follow up visit one year later, the patient was totally asymptomatic.

Discussion

The majority of patients with iliac artery aneurysms are first seen by an internist, more commonly by a gynecologist or urologist with symptoms such as dysuria, frequency or renal colic. The aneurysms are usually asymptomatic and rarely suspected on pelvic or rectal examinations unless an expansile pulsatile mass is felt. They become symptomatic secondary to progressive enlargement causing displacement, compression or occlusion of the organs in

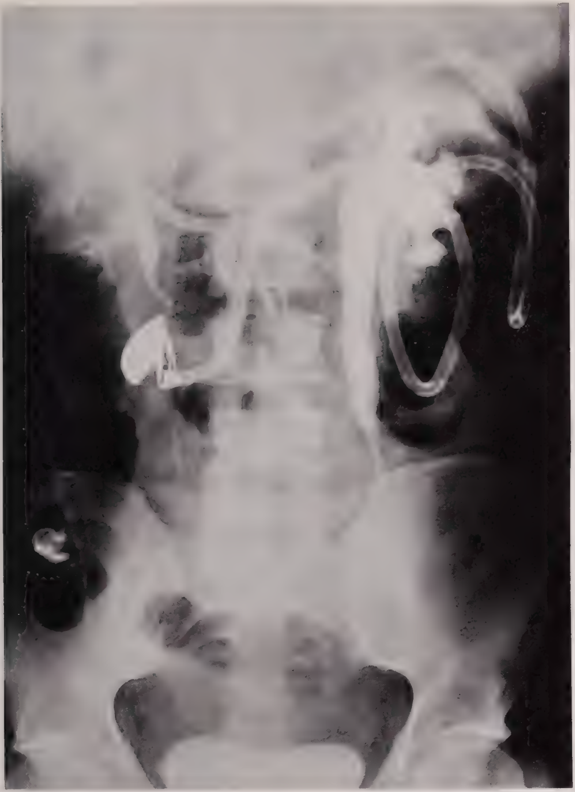

FIG. 5. Preoperative I.V.P. demonstrating the large left hydroureter.

their vicinity. Occasionally, the main presentation is tenesmus due to the displaced rectum, claudication or swelling of the lower extremity as the result of compressed iliac veins (1, 2). IVP may demonstrate hydronephrosis, a nonfunctioning kidney or bladder displacement.

Iliac artery aneurysms are usually not considered in the differential diagnosis of pelvic masses and therefore are commonly diagnosed only at celiotomy. They are only one-tenth as common as aneurysms of the abdominal (3, 4) aorta and although an arteriogram may be diagnostic, the miniscule incidence of this aneurysm in comparison to other pelvic masses probably does not

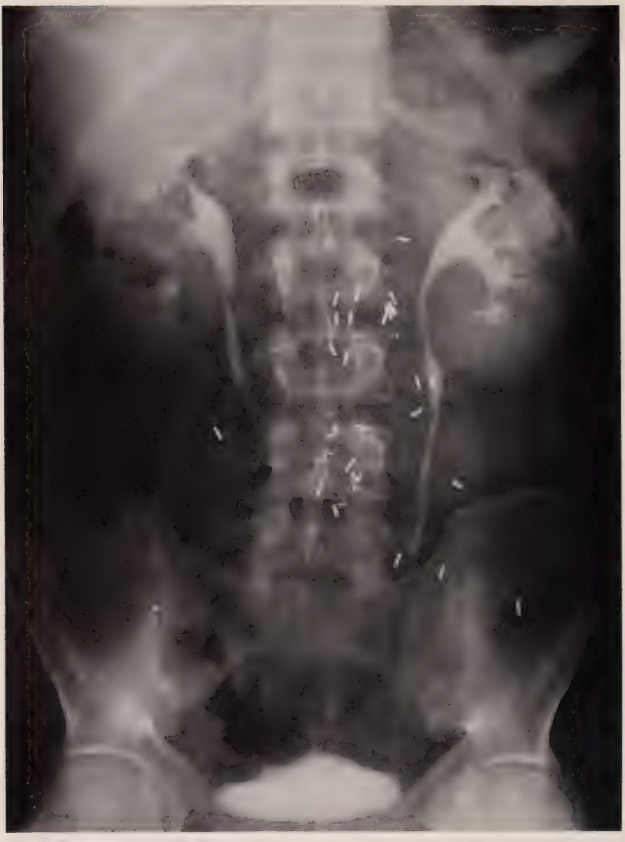

FIG. 6. Postoperative I.V.P. (2 months) complete resolution of the obstructive uropathy.

justify its use routinely. It should be reserved for the suspected cases, especially in the elderly, when the sonogram is positive, and in those who demonstrate a calcific rim on abdominal x-rays.

Some of the cases are diagnosed intraoperatively. If the findings at celiotomy are of hypogastric artery aneurysm, ligation of the neck should be performed. If, on the other hand, a major vascular procedure is required in an unprepared patient, the procedure should be postponed until complete workup has been carried out.

Hydroureter, when present, is the result of encasement and fixation of the ureter in the dense, fibrotic aneurysmal wall, as well as compression by the enlarging mass against the pelvis (5, 6). Management depends largely on the extent of the fibrotic changes, the technical feasibility, the condition of uninvolved kidney and general status of the patient. The best surgical correction for the particular patient may be extremely difficult. Our two cases illustrate that judicious exercise of clinical judgement is indeed important.

Ligation of the neck of the hypogastric aneurysm without ureterolysis should relieve the ureteral compression as in our first case. If the ureter is totally encased in the desmoplastic reaction, lysis will achieve decompression as in our second case (6, 7). If lysis carries a great risk of ureteral injury, it should not be pursued especially if insertion of a graft is contemplated because of the danger of bacterial contamination (2).

In cases where the contralateral kidney is absent or its function compromised, and the involved ureter is severely encased in fibrotic tissue, probably ureteral lysis is a necessary procedure in order to preserve the function of at least one kidney.

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Renal Hydrogen Ion Secretion and Excretion during Acute Acid Loading

ALAN J. DIAMOND, M.D.* AND MICHAEL W. WEINER, M.D.

Abstract

Acute administration of an acid load results in prompt acidification of the urine, associated with a rise in NH_4^+ and titratable acid excretion. One possible mechanism of urinary acidification is that intracellular acidosis stimulates H^+ secretion by the nephron. Alternatively, a lowered filtered load of HCO_3^- may reduce the secreted H^+ consumed by HCO_3^- reabsorption, thus increasing the supply of H^+ for formation of urinary ammonium and titratable acid. The latter appears to predominate in established severe metabolic acidosis; total urinary acid excretion is high, while total renal H^+ secretion is diminished. In order to characterize the mechanism of urinary acidification during the onset of metabolic acidosis, 6 normal unanesthetized dogs were infused with HCl (43 μmole/kg body weight/min) while measurements of arterial blood gases, GFR, and urinary acid excretion were simultaneously performed. The initial response to acid infusion was a fall in plasma HCO_3^-, thereby diminishing the filtered load of this anion. Urine pH did not fall nor did acid excretion rise, until H^+ secretion had diminished by 7–20% from control values. Acidosis also induced an increased urinary excretion of Na^+, K^+, Ca^{++}, and Mg^{++}. We conclude that acute metabolic acidosis does not stimulate tubular H^+ secretion. Rather, urinary acidification appears to be induced by the enhanced fraction of secreted H^+ made available for urinary acid excretion.

Introduction

The administration of an acid load to man and experimental animals results in urinary acidification (i.e., a fall in urinary pH), associated with a rise in net urinary acid excretion in the form of NH_4^+ and titratable acid (1–5). However, the mechanism by which metabolic acidosis produces acidification of the urine is not completely understood. Since the amount of acid excreted in the urine greatly exceeds the amount filtered, H^+ must be secreted by the renal tubular cells. This H^+ transport appears to occur against an electrochemical gradient; therefore, an active H^+ "pump" has been postulated (6–11). Stimulation of this H^+ secretory process is one possible mechanism by which metabolic acidosis could lower the urinary pH. Another possible mechanism involves alterations in the amount of secreted H^+ available for urinary excretion (12): most of the

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H^+ secreted by the kidney is utilized for the reabsorption of filtered HCO_3^- (13). Metabolic acidosis produces a fall in the blood HCO_3^- content, thereby diminishing the filtered load of this buffer anion. This diminished filtered load reduces the amount of secreted H^+ necessary for HCO_3^- reabsorption, thereby leaving more H^+ available for urinary excretion as titratable acid and NH_4^+. During severe metabolic acidosis the rate of H^+ secretion must be markedly reduced, secondary to a decreased filtered load of HCO_3^-. In this condition stimulation of the H^+ pump would not be detectable. However, the sequence of events occurring during the initial development of mild acidosis, where increased H^+ secretion could be measured, has not been adequately studied.

In order to determine the relative importance of HCO_3^- filtration and H^+ secretion in the control of urinary acid excretion, we have investigated the early sequence of events during the induction of metabolic acidosis in unanesthetized dogs. The results indicate that urinary acidification induced by systemic metabolic acidosis results from a diminished rate of HCO_3^- reabsorption. This increases the amount of secreted H^+ available for urinary acid excretion. Stimulation of net renal H^+ secretion does not appear to participate in the initial response to acute metabolic acidosis.

Methods

Seven female mongrel dogs with weights ranging from 17 to 31 kg were utilized. One week prior to the acid-infusion experiments, an indwelling polyethylene catheter was surgically inserted into the left external jugular vein and passed 15 to 22 cm into the superior vena cava. The catheter was secured to the jugular vein, passed under the skin, and exteriorized through the dorsal aspect of the neck. Clot formation was prevented by daily flushing with heparinized saline. An episiotomy was performed to facilitate the subsequent insertion of a urethral catheter. The dogs were maintained on Wayne dry food diet and water *ad libitum*. One dog (S) was fed canned meat the day prior to the experiment. On the day of the experiments the dogs were lightly anesthetized with intravenous sodium pentothal (25 mg/kg). A polyethylene catheter was inserted into the left femoral artery for collection of arterial blood, and a #14 Foley catheter was placed in the bladder. The dogs were then suspended in a canvas sling (in which they had been previously trained to stand) for the remainder of the experiment.

When the dogs became fully conscious ($t = -105$ min), the infusion protocol was begun (Fig. 1). In order to prevent prolonged contact between the acid and the clearance substances (inulin, para-amino-hippurate [PAH], or creatinine), the acid solutions were prepared and infused separately. The tubes leading from the solution containers were connected by a common drip chamber, thereby reducing the total contact time between strong acid and clearance substances to less than 30 seconds before entering the indwelling venous catheter. Initially, a solution of 150 mM sodium chloride, 25 mM potassium chloride, and 5% mannitol (Na, K-mannitol) was infused at 4 ml/min. When the urine flow exceeded 2.5 ml/min (approximately $t = -75$ min), intravenous priming doses of PAH and inulin were administered to dogs

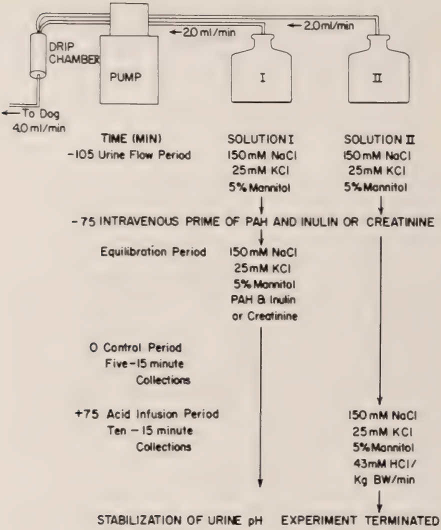
←2.0 ml/min
←2.0 ml/min
DRIP CHAMBER
PUMP
I
II
←To Dog 4.0 ml/min
TIME (MIN)
SOLUTION I
SOLUTION II
−105 Urine Flow Period
150 mM NaCl
25 mM KCl
5% Mannitol
150 mM NaCl
25 mM KCl
5% Mannitol
−75 INTRAVENOUS PRIME OF PAH AND INULIN OR CREATININE
Equilibration Period
150 mM NaCl
25 mM KCl
5% Mannitol
PAH & Inulin or Creatinine
0 Control Period
Five–15 minute Collections
+75 Acid Infusion Period
Ten – 15 minute Collections
150 mM NaCl
25 mM KCl
5% Mannitol
43 mM HCl/Kg BW/min
STABILIZATION OF URINE pH
EXPERIMENT TERMINATED

FIG. 1. Acid infusion protocol.

U, V and R. Dogs Z, S, Y, and AA (control receiving no acid) received creatinine instead of inulin. Immediately following the prime, sustaining solutions of the clearance substances in Na,K-mannitol were infused to maintain plasma levels close to optimum for clearance determinations. Na,K-mannitol was infused at 4 ml/min through the experiment. At t = 0 min, 15 min control collections of urine and arterial blood were begun. After four-five control collection periods HCl was infused at 43 μmoles/kg body weight/min for 150–200 min, while 15 min collection periods were continued. The experiments were terminated when the urine pH remained constant for two consecutive periods or after four hours of HCl infusion. By this time, all dogs were severely acidotic.

Urine samples were anaerobically collected under mineral oil to insure minimal CO_2 loss. Urine pH was determined at 39°C (dog core temperature equals 39°C) using a Beckman Research Meter Model #19 pH meter, standardized at pH 7.4, 7.0, 6.0, and 4.0 (Beckman pH standard solutions). Titratable acid (TA) was determined by titration to pH 7.4 with 0.001 N NaOH.* Urine samples were sealed in 1.0 ml syringes for the measurement of total bicarbonate using a Natelson Microgasometer. Urine samples were also frozen for subsequent chemical analysis. Ten ml of arterial blood was collected at the end of each period in heparinized syringes from the left femoral artery catheter. Arterial blood pH and pCO_2 were immediately determined with an Instrumentation Laboratories pH pCO_2/pO_2 Electrometer (Model 113-SI) standardized at 39°C. The pH electrode was standardized at pH 7.384 and 6.84 immediately before each determination. The pCO_2 was standardized with 4.11% and 8.00% CO_2. The remaining 8 ml of blood was centrifuged immediately, and the plasma was frozen for subsequent chemical analysis.

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* Aerobic titrations of urine samples in the neutral or alkaline range result in an increase in urine pH during the procedure due to the loss of CO_2 on exposure to air. This effect decreases the apparent titratable acidity. In order to reduce this error, samples were sealed until the titrations were performed.

Inulin, creatinine and PAH in fresh plasma and urine were determined utilizing a Technicon AA2 Autoanalyzer. Na^+ and K^+ in the plasma and urine were measured with an Instrumentation Laboratories Flame Photometer. Cl^- was measured with an Aminco-Cotlove Chloride Titrator. Ca^{++} and Mg^{++} were determined with a Perkin Elmer Atomic Absorption Spectrophotometer. Urinary NH_4^+ was determined by the Berthelot reaction (14).* Urinary PO_4 was measured by the Sumner method (15).

Calculations: The concentration of plasma bicarbonate was calculated from pCO_2 and pH using the Henderson-Hasselbach equation:

$$\text{Plasma } HCO_3^- = (s \cdot pCO_2)\ (\text{Antilog pH} - pK)$$

The pK was derived from the blood pH, and a solubility coefficient (s.) of 0.0294 was used for blood at 30°C (16). Urinary HCO_3^- was also calculated from the Henderson-Hasselbalch equation:

$$\text{Urine } HCO_3^- = \text{Total } CO_2 - s \cdot pCO_2$$

where

$$s.\ pCO_2 = \frac{\text{Total } CO_2}{[(\text{Antilog pH} - pK) + 1]}$$

where

$$\text{Urine } pK = 6.32 - 6.0\ \sqrt{u}^{17}$$

Total ionic strength (u), calculated from the urinary values of Na^+, K^+, NH_4^+, PO_4, Cl^-, and HCO_3^-; ranged from 0.1–0.7. The glomerular filtration rate (GFR) was calculated from the clearance of inulin or creatinine. PAH clearance was used to estimate renal plasma flow (RPF). Other values were calculated as follows:

$$\begin{aligned}
\text{Filtration fraction} &= \text{GFR/RPF} \\
\text{Filtered}_{HCO_3^-} &= \text{Arterial}_{HCO_3^-} \times \text{GFR} \\
\text{Reabsorbed}_{HCO_3^-} &= \text{Filtered}_{HCO_3^-} - \text{Urinary}_{HCO_3^-} \\
\text{Total urinary acid excretion (3)} &= \text{Urine}_{NH_4^+} + \text{Urine}_{TA} + \text{Urine}_{\text{Free } H^+} \\
\text{Total renal } H^+ \text{ secretion} &= \text{Total urinary acid excreted} \\
&\quad + \text{reabsorbed}_{HCO_3^-}
\end{aligned}$$

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* Although the Berthelot reaction measures the sum of NH_4^+ and NH_3, the amount of NH_3 present in urine at physiological pH is negligible (1).

Results

General effects: The direct intravenous infusion of large amounts of hydrochloric acid 150–300 mmoles H^+) was tolerated by all dogs. During the first 90 min of acid infusion, no gross detrimental effects were noted. Acid administration caused the GFR of dogs Z, V, S, and R to fall as much as 15% from control values. In dogs Z and V, the GFR promptly returned to control values; in S and R it remained somewhat depressed (Table II). Near the end of the experiment, several dogs appeared to hyperventilate. Dog U vomited, prompting immediate termination of the experiment. Plasma samples remained straw-colored throughout all experiments, indicating that infusion of HCl directly into the vena cava did not cause gross hemolysis of blood. At the end of the experiments, all dogs appeared to be extremely thirsty.

In order to insure that alterations in acid-base and electrolyte homeostasis were solely due to acid infusion, a control experiment without acid administration was performed (dog AA). All other experimental details were otherwise identical to the acid loading protocol. During this 210 min control experiment, urine and blood values remained relatively constant. Blood pH remained above 7.40, blood pCO_2 remained above 30 mm Hg, and blood HCO_3^- fluctuated between 21–24 mM. Urine pH varied between 6.92–7.20 and HCO_3^- excretion fluctuated between 35–70 μmoles/min. In contrast, to the acid loading experiments, urine volume decreased slightly from 5.5 ml/min to 4.3 ml/min. GFR and RPF remained constant throughout the experiment. Serum K^+ rose slightly from 4.0 mM to 4.5 mM while urine K^+ excretion fluctuated with no consistent trend. Ca^{++} and Mg^{++} excretion decreased slightly.

Effects of acute metabolic acidosis on acid-base homeostasis (Tables I and II, Figure 2): The effects of intravenous acid infusion on dog U are depicted in Table I. Prior to acid infusion (periods 1–4) this animal had a blood pH ranging from 7.40 to 7.43 and a blood HCO_3^- of 17.1 mM to 21.8 mM. There were few significant fluctuations during the control periods, although the blood HCO_3^- and pCO_2 dropped slightly during period 4. During the first collection period following the initiation of the acid infusion (period 5) blood pH decreased very slightly to 7.39 while the pCO_2 and HCO_3^- remained within the control values. The urine pH also stayed very close to control, but the rate of HCO_3^- excretion was slightly diminished. Although urinary excretion of NH_4^+ and total acid (12.83 μmoles/min) rose slightly, the total amount of H^+ secreted (1901 μmoles/min) did not change. In period 6 the urine pH decreased significantly; this was associated with a diminished HCO_3^- excretion and a rise in the rate of urinary NH_4^+ and total H^+ (17 μmoles/min) excretion. However, the rate of H^+ secretion remained unchanged from control values (1951 μmoles/min). By period 7, blood pH was 7.37 and the blood HCO_3^- had dropped to 16 mM. At this time, the rate of urinary H^+ excretion had doubled from control values to 2149 moles/min. Nevertheless, the total H^+ secreted had fallen to 1820 μmoles/min, an amount lower than previous values. During the following periods, the changes were more dramatic. Blood pH and HCO_3^- decreased markedly. Concurrent reductions in urine pH and urine HCO_3^- also occurred.

TABLE I

Effects of Acid Infusion on Dog U

Collection Period*	Blood††			GFR (ml/min)	Urine							Filtered† HCO_3 (μmol/min)	Reab-sorbed HCO_3 (μmol/min)	Secreted† H^+ (μmol/min)
	pH	PCO_2 (mmHg)	HCO_3 (mM)		Vol (ml/min)	pH	PO_4 (μmol/min)	Tit. Acid (μmol/min)	NH_4^+ (μmol/min)	Total† H^+ (μmol/min)	HCO_3 (μmol/min)			
1	7.400	36.3	21.8	100	4.73	7.345	0.0059	0.0	10.22	10.22	105	2180	2075	2085
2	7.434	32.4	21.1	105	4.73	7.321	0.0060	0.0	10.13	10.13	98	2216	2118	2128
3	7.404	31.2	18.9	117	5.13	7.325	0.0053	0.0	11.60	11.60	97	2211	2114	2126
4	7.425	26.8	17.1	115	5.13	7.322	0.0065	0.0	11.91	11.91	96	1966	1870	1882
Begin infusion of 43 μmol HCl/kg BW/min.														
5	7.390	30.8	18.1	109	4.73	7.315	0.0055	0.0	12.83	12.83	84	1972	1888	1901
6	7.380	32.0	18.3	109	4.27	7.181	0.0039	0.0	17.02	17.02	61	1995	1934	1951
7	7.372	28.5	16.0	115	4.13	7.195	0.0031	0.0	21.49	21.49	41	1840	1799	1820
8	7.395	25.8	15.3	120	4.67	7.090	0.0025	0.0	25.01	25.01	41	1836	1795	1820
9	7.320	29.2	14.4	121	5.47	7.132	0.0031	0.0	26.13	26.13	56	1742	1686	1712
10	7.270	26.6	11.7	151	6.75	7.123	0.0048	0.0	28.35	28.35	75	1767	1692	1720
11	7.305	22.2	10.6	144	7.20	7.134	0.0061	0.0	27.36	27.36	75	1526	1451	1478
12	7.203	29.0	10.8	116	6.67	6.995	0.0065	0.0	32.60	32.60	56	1253	1197	1229
13	7.189	24.3	8.8	98	5.47	6.966	0.0067	0.0	30.39	30.39	34	862	828	858
14	7.169	22.2	7.5	124	6.67	6.850	0.0096	0.40	46.47	46.87	30	930	900	947
15	7.140	20.0	6.4	132	6.80	6.336	0.0143	5.30	56.92	62.22	15	845	830	892

* Each period = 15 min.

† See calculations.

†† Blood values correspond to the end of each collection period.

TABLE II

Effects of Acid Infusion on Five Dogs

Period	pH	Blood††		Urine									
		PCO_2 (mm/Hg)	HCO_3 (mM/l)	GFR (ml/min)	Volume (ml/min)	pH	Acid (μmol/min)	NH_4^+ (μmol/min)	Total† H^+ (μmol/min)	HCO_3 (μmol/min)	Filtered† HCO_3 (μmol/min)	Reabsorbed HCO_3 (μmol/min)	Secreted† H^+ (μmol/min)
						DOG U							
Control*:													
x	7.42	31.68	19.73	109.25	4.93	7.31	0	11	11	99.0	2143.25	2044.25	2055.25
SE	0.007	1.96	1.07	4.05	0.1154	0.02	0	0.46	0.46	2.04	59.62	58.89	58.59
1.	7.39	30.8	18.1	109.0	4.73	7.40	0	12.8	12.8	84.0	1972.0	1888.0	1901.0
2.	7.38	32.0	18.3	109.0	4.27	7.18	0	17.0	17.0	61.0	1995.0	1934.0	1951.0
3.	7.372	28.5	16.0	115.0	4.13	7.20	0	21.3	21.5	41.0	1840.0	1799.0	1820.0
4.	7.395	25.8	15.3	120.0	4.67	7.09	0	25.0	25.0	41.0	1836.0	1795.0	1820.0
						DOG R							
Control**:													
x̄	7.37	28.98	16.25	93.75	5.28	7.141	0.278	9.04	9.32	85.71	1522.5	1436.75	1446.0
SE	0.0096	1.96	0.284	1.72	0.231	0.070	0.198	0.85	0.97	2.53	26.9	25.47	24.84
1.	7.36	27.5	15.0	88.0	5.53	6.98	1.22	10.0	11.2	78.2	1320.0	1242.0	1253.0
2.	7.312	28.0	13.6	94.5	5.67	7.00	1.02	12.1	13.2	75.1	1272.0	1197.0	1210.0
3.	7.285	27.0	12.3	86.8	5.33	6.83	2.61	15.3	17.9	48.2	1055.0	1007.0	1025.0
4.	7.255	27.5	11.6	87.0	5.80	6.73	3.89	20.9	24.8	46.7	1009.0	962.0	987.0
						DOG Z							
Control**:													
x̄	7.40	33.58	20.07	162.5	3.69	7.04	0	38.64	38.64	42.67	3172.0	3230.25	3269.0
SE	0.009	1.23	0.46	11.087	0.35	0.07	0	6.52	6.52	5.1	375.0	372.05	277.41
1.	7.405	35.0	21.25	137.0	3.53	7.02	0	33.84	33.83	42.40	2911.0	2869.0	2903.0
2.	7.398	33.5	20.01	150.0	3.97	6.96	0	46.89	46.89	34.31	3002.0	2968.0	3015.0
3.	7.345	34.5	18.12	121.0	3.53	6.67	0	44.45	44.77	18.23	2193.0	2145.0	2188.0
4.	7.355	31.5	16.93	146.0	4.83	6.60	0	73.41	73.80	16.64	2472.0	2455.0	2529.0

DOG Y

Control**:												
x̄	7.396	36.2	21.52	133.51	4.55	6.88	7.13	30.09	37.42	20.2	2877.2	2857.0	2892.4
SE	0.003	0.96	0.69	2.21	0.103	0.09	4.07	4.19	7.97	6.96	133.03	108.0	102.71
1.	7.40	34.5	20.71	144.9	4.87	7.11	0	17.71	17.71	70.0	2980.0	2910.0	2928.0
2.	7.398	34.0	20.31	144.0	4.83	7.20	0	17.59	17.59	74.0	2931.0	2857.0	2875.0
3.	7.345	36.0	18.90	139.2	4.47	7.13	0	21.71	21.71	58.0	2631.0	2573.0	2595.0
4.	7.354	31.0	16.62	141.9	4.47	6.76	1.47	25.91	27.38	20.0	2342.0	2322.0	2349.0

DOG S

Control**:													
x̄	7.41	30.13	18.56	102.95	5.54	7.52	0	11.1	11.1	175.5	1913.25	1738.0	1748.55
SE	0.007	0.27	0.47	2.25	0.095	0.05	0	0.73	0.73	3.66	83.2	83.21	84.06
1.	7.41	27.0	16.58	103.0	5.0	7.6	0	10.65	10.65	159.0	1708.0	1549.0	1560.0
2.	7.43	27.9	17.99	109.4	4.77	7.55	0	9.21	9.21	148.0	1968.0	1820.0	1829.0
3.	7.365	23.6	13.01	91.2	4.73	7.6	0	7.95	7.95	125.0	1180.0	1055.0	1063.0
4.	7.32	26.5	13.11	90.0	4.53	7.50	0	12.37	12.37	99.0	1178.0	1079.0	1090.0

Despite dramatic increases in NH_4^+ excretion and total H^+ excretion, H^+ secretion continued to fall at a rapid rate. By the termination of the experiment (period 15) the H^+ excretion had risen to six times control values (62.2 μmoles/min) while total H^+ secretion fell to less than half of the control rates (892 μmoles/min).

Similar studies were performed on five other dogs (Table II). In each case urine pH did not significantly fall, nor did acid excretion significantly rise, until H^+ secretion had diminished 7% to 20% from control values. The relationship between renal H^+ secretion and urinary acid excretion for all six experimental dogs is summarized in Figure 2. In order to meaningfully compare these diverse values, both renal H^+ secretion and urinary acid excretion have been divided by GFR and expressed as a percentage of the mean control values, represented at time zero. During the first 15 min acid infusion period, mean total H^+ secretion was diminished to 96 ± 3% of control, whereas acid excretion was also slightly lowered. After 30 min of acid infusion, urinary acid excretion had begun to rise; at this time renal H^+ secretion was depressed to 90 ± 4% of control. Throughout the remainder of the experiment, urinary excretion of total acid progressively increased, while renal H^+ secretion steadily decreased. After 165 min of acid loading, mean urinary acid excretion rose by 550%; H^+ secretion diminished to 46% of control.

Effects of acid loading on urinary excretion of Na^+ and water: Acid loading had a variable effect on urinary volume and Na^+ excretion. The control dog (AA) showed a slightly decreased urine output with a diminishing Na^+ content. Dogs S and Y demonstrated no change in these parameters during acid loading. The four other dogs all developed a diuresis in response to systemic acidosis.

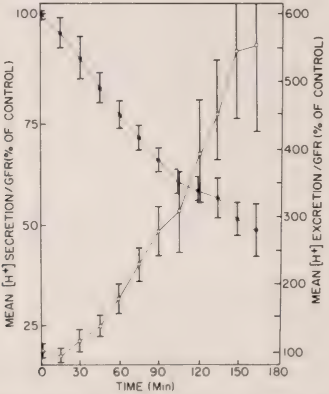

FIG. 2. Summary of effects of acid loading on urinary acid excretion (○) and renal hydrogen ion secretion (●) of six experimental dogs. Both urinary acid excretion and renal H^+ secretion are divided by GFR and are expressed as a percentage of mean control values represented at time zero. Acid infusion begins at time zero. Data are expressed as the mean ± standard error.

After 210 min of acid infusion, mean urine output rose from the control rate of 4.3 ml/min to 6.4 ml/min. Urinary sodium excretion also rose in the same four dogs by 30% to 400% of control values. Since severe metabolic acidosis usually depressed GFR, the rise in fractional excretion of sodium was even more impressive, increasing by as much as 240%. This could not be accounted for by a change of plasma Na^+ which remained fairly constant. Prior to acid loading, urinary losses equaled fluid input. Therefore, volume expansion could not be responsible for the natriuresis. The rise in sodium excretion showed no correlation with GFR, RPF, or filtration fraction. However, an excellent correlation between the severity of acidosis and degree of natriuresis was noted in dogs R and V who showed a rise of fractional excretion of sodium from a mean of 2.8% to 8.6%. For these two dogs, correlation coefficients (r) were highly significant between fractional excretion of sodium and blood pH (mean r for these dogs was 0.843, $p < 0.001$), reabsorbed HCO_3^- (mean $r = 0.873$, $p < 0.001$), and total acid excretion (mean $r = 0.884$, $p < 0.001$).

Effects of acid loading on K^+ excretion: Intravenous infusion of acid had dramatic effects on K^+ content of blood and urine. As anticipated, plasma K^+ promptly rose from control values while systemic acidosis developed. In contrast to the expected finding, urinary potassium excretion was also enhanced. Figure 3 summarizes these findings for the 6 experimental animals. After 60 min of acid infusion, K^+ excretion began to increase markedly despite urinary acidification. Although urinary K^+ excretion rose as high as 0.48 μmoles/min (from control values of 0.07 to 0.21 μmoles/min), it never surpassed the filtered load; therefore, stimulation of net secretion could not be established. A strong correlation between urinary K^+ excretion and Na^+ excretion was noted in 4 dogs; the mean r was 0.852, $p < 0.01$ for each dog.

Effects of acid loading on excretion of divalent cations: Systemic metabolic

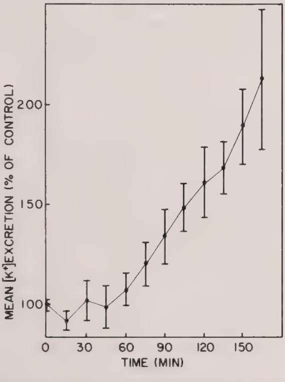

FIG. 3. Effects of acid loading on urinary K^+ excretion. Data are expressed as a percentage of mean control values represented at time zero. Acid infusion begins at time zero. Data are expressed as the mean ± standard error.

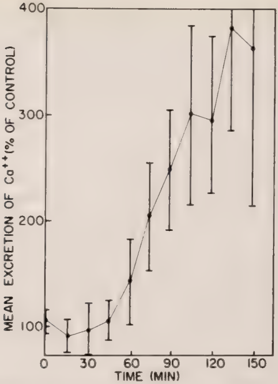

FIG 4. Effects of acid loading on urinary Ca^{++} excretion. Data are expressed as a percentage of mean control values represented at time zero. Acid infusion begins at time zero. Data are expressed as the mean ± standard error.

acidosis prompted enhanced urinary excretion of Ca^{++}. Figure 4 summarizes the results with all six experimental dogs. After 60 min of acid infusion, mean excretion of Ca^{++} began to rise markedly, achieving a rate greater than three times control values. Ca^{++} excretion correlated well with urinary Na^+ for the same 4 dogs showing a relationship between urinary Na^+ and K^+ excretion; the mean r was 0.827, $p < 0.01$ for each dog. Mg^{++} excretion also rose substantially in all dogs except S. The extent of rise varied from 45% to 208% of control after 210 min of acid infusion. Changes in urinary PO_4 excretion varied greatly. There was no correlation with alterations of GFR, RPF, or filtration fraction; severity of acidosis; or excretion of Na^+, Ca^{++}, Mg^{++}, or Cl^-.

Discussion

Systemic metabolic acidosis induces an immediate increase in free H^+ content of the urine, which is in turn associated with a rise in NH_4^+ and titratable acid excretion (2–5). Although the latter events have been thoroughly studied (2–5, 19–21) the mechanism by which systemic acidosis results in urinary acidification remains unclear. One possibility is that the pH of the extracellular fluid regulates the rate of H^+ transfer from the renal cell into the lumen (8–9). Acidosis would stimulate the "H^+ pump" resulting in acidification of the luminal contents. Alternatively, Rector (12) has proposed that metabolic acidosis reduces the filtered load of bicarbonate and diminishes the secreted H^+ utilized for HCO_3^- reabsorption, thus enhancing the supply of H^+ for urinary excretion. Although many previous studies of acid loading have been reported (2–5, 19–21), none have quantitated renal H^+ secretion and urinary acid excretion during the onset of metabolic acidosis.

The results presented in this report clearly demonstrate that the initial response to an acid load is a decrease in the filtered load of HCO_3^- followed shortly by a decrease in urinary pH and a rise in total acid excretion. Since most of the H^+ secreted by the kidney is utilized for HCO_3^- reabsorption (13), systemic acidosis initially induces a decrease in renal H^+ secretion. At first, these findings may seem physiologically paradoxial because acid excretion rises in the face of diminished H^+ secretion. Nevertheless, this system allows a renal response to metabolic acidosis which is not directly dependent upon metabolic or hormonal alterations. It is based upon the fact that HCO_3^- is reabsorbed by non-ionic diffusion as CO_2, in response to a pH gradient. Reabsorption of HCO_3^- results in an increased luminal H^+ concentration. This luminal H^+ in turn favors both the trapping of NH_4^+ (which also is transferred by non-ionic diffusion as NH_3 towards the more acid compartment) as well as the formation of titratable acid in the tubular lumen.*

In contrast to acute metabolic acidosis, a marked rise in renal H^+ secretion has been demonstrated in chronic metabolic acidosis (1). This increase is largely due to enhanced renal production of NH_4^+ (1) and is not necessarily caused by direct activation of the "H^+ pump". Stimulation of the "H^+ pump" is not ruled out by our results. It is possible that in certain nephron segments (especially the most distal portions) H^+ transport is stimulated or is continued against an increasing electrochemical gradient.

The diuretic effects of acidifying salts have been recognized for many years (22–27), but not completely characterized. Rector (28) and Kokko (29) have suggested that proximal Na^+ reabsorption is linked to HCO_3^- transport; a diminished filtered load of HCO_3^- would thus impair proximal reabsorption of Na^+ (30–33). Another possibility is that the elevation of filtered Cl^- produced by HCl administration would saturate the Cl^- transport system of the ascending limb of Henle's loop (34–35). Finally, metabolic acidosis might inhibit cellular energy production or utilization for ion transport. In any case the magnitude of natriuresis would be expected to correlate with the severity of acidosis, a suggestion confirmed by our results.

Urinary K^+ excretion rose in all dogs during the development of metabolic acidosis. This finding contrasts with the generally accepted view that respiratory (36) or metabolic acidosis (36–37) curtails K^+ excretion by diminishing tubular secretion of this ion (38). If the natriuresis induced by acidosis results from an inhibition of proximal or ascending limb solute and water reabsorption, the increased delivery of Na^+ and water to the distal tubule might result both in a greater flow rate and a decreased potential difference in this nephron segment, thus stimulating K^+ secretion (38).

Metabolic acidosis produced a progressive rise in urinary losses of the divalent cations Ca^{++} and Mg^{++}. These findings are in agreement with many previous reports (39–43). Several mechanisms may be invoked, including a direct action on bone (39–40) or inhibition of renal reabsorption (43). However, the strong correlation presently demonstrated between Na^+ and divalent cation excretion is similar to that reported by other workers under different experimental conditions (44–50). This suggests that inhibition of Na^+ transport may have been responsible for the increase in Ca^{++} and Mg^{++} excretion.

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* Barker et al (18) have expressed urinary acid excretion as: $\text{Urinary}_{NH_4^{++}}$ Urinary_{TA} + $\text{Urinary}_{\text{Free } H^+}$ − $\text{Urinary}_{HCO_3^-}$. Although this concept reflects total acid-base economy, the appearance of HCO_3^- in the urine solely represents that which has escaped reabsorption. Urinary HCO_3 gives no direct indication of tubular H^+ secretion or acid excretion per se.

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Histamine Release in Clinical Conditions*

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Histamine release in man can be shown by direct and by indirect methods (1). The direct methods include histamine assays in various body fluids (1). Mostly they use principles of pharmacokinetics demonstrating increase and decrease of histamine concentrations corresponding or very similar to the Bateman function (2). They include histamine determinations in whole blood, in cells isolated from blood such as leucocytes, basophils or thrombocytes, and in tissues such as lung, skin or biopsies of the gastrointestinal tract. The second group of methods mostly demonstrates a decreased content of histamine which is discharged from its stores. Either the free, biologically active histamine is determined not directly by these methods, or they need an artificial incubation medium which may not really correspond to the clinical situation. Furthermore they often are afflicted with tissue injury, hypoxia and acidosis, and they mostly do not allow to measure the kinetics of the release process.

The indirect methods include estimations of the biological effects of histamine, such as gastric acid secretion, tachycardia, delayed depressor response of the peripheral blood pressure etc. These reactions should be inhibited by H_1- and H_2-receptor antagonists in vivo. The indirect methods, however, are rather unspecific. Thus there is no doubt that from all methods for measuring histamine release in man the plasma histamine assay at present is the most direct one, and is used under conditions which are nearest to the physiologic and pathological situations to be investigated (1).

Methods for Plasma Histamine Determination

At present there are two principle methods which possess a satisfactory reliability for plasma histamine determination. The one is the fluorometric assay of the amine following ion-exchange chromatography on Dowex 50 and subsequent butanol extraction (2), the other is the enzymatic double-isotope dilution method using histamine methyltransferase (3).

These two techniques are considered reliable since the criteria for testing the reliability of clinical chemical methods have been strictly applied to them and have been shown to be sufficiently fulfilled (1–5).

The sensitivity of the fluorometric assay as defined by clinical chemistry (6)

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has been increased considerably in the last seven years (2, 7, 8). Using the standard incubation mixture with o-phthaldialdehyde (about 3 ml) it is now high enough to measure still 100 pg histamine/ml plasma. However, sensitivity has been increased in this laboratory to about five-fold (21 pg/ml) by modifying the reaction conditions (8a). Such a sensitivity at present is not often necessary for measuring histamine release. Basic research scientists should learn to work with a more practical definition of sensitivity using Bayes's theorem (9): The sensitivity of a test is the number of subjects with a disease who show a positive result in the test for diagnosing this disease. The optimum is 100 percent; more "sensitivity" is analytical narcissism. Furthermore the errors in sample-taking and sample-preparing of plasma sometimes are in the nanogram range (1, 8) and seem to be more important for impairing the reliability of the assay than those of the analytical procedure itself.

The specificity of the fluorometric method for plasma histamine assay is satisfactorily demonstrated (2, 4, 8). The tests on identity of histamine as the only substance being measured in human plasma by fluorescence include fluorescence spectra at 0° and 21° C, heating test with spectra recorded, formaldehyde test and inactivation of the amine by purified histamine methyltransferase and purified diamine oxidase (measuring reaction kinetics) (1). The main criterion for specificity of the enzymatic isotope assay is the use of highly specific histamine methyltransferase in the procedure. It should be pointed out that our fluorometric assay is examined by the same criterion and also by the others mentioned above. Thus the argument of a lesser specificity of our fluorometric assay than that of the enzymatic isotope assay is no longer valid.

The precision of the fluorometric method for human plasma histamine concentration has been tested under the conditions of histamine release. 40 volunteers (32 male, 8 female, age 21–37) were treated by a small dose of exogenous histamine (600 ng/kg) as an intravenous injection, 20 mins. later by a blood donation of 500 ml and thereafter the infusion of 500 ml Haemaccel which is a plasma substitute and releases small amounts of histamine in man under normal clinical conditions (11). Blood for plasma preparation was collected at various times of this investigation and pooled. Two samples of this plasma pool were assayed on every occasion when plasma histamine levels in patients were determined in the next few months. The histamine concentration of this control plasma was 3.3 ng/ml. The coefficient of variation within-day was 7.2 percent ($n = 10$). Quality control during the 3 months of the study was possible. No values were out of action limits, no trends were observed.

The accuracy of the fluorometric assay for human plasma histamine was tested by two criteria: (1) Mixing aliquots of plasma with low and high histamine concentrations showed a straight line. (2) Histamine values obtained by fluorometry corresponded to those reported by authors using other techniques, especially the enzymatic isotope assays (Table I).

It has been assumed that the fluorometric assay is time-consuming and tedious because it includes an ion-exchange and an extraction step. But these two steps can be standardized and simplified to a large extent (4). At present

TABLE I

Plasma Histamine Concentrations in Human Subjects Measured by Several Methods

Histamine concentrations mean and range [ng/ml]		Principle of the method	Reference
—	(0–1.0)	Bioassay	12
0.62	(0.1–1.4)	Fluorometry	13
—	(0.3–1.4)	Fluorometry	2
0.61	(0.4–1.0)	Isotope	14
<0.5		Isotope	3
0.5	(0–1.1)	Fluorometry	1
0	(0–0.3)	Fluorometry	15
0.46	(0–1.24)	Isotope	16
0.3	(0–0.9)	Fluorometry	This paper

routinely about 25–30 samples of plasma are analysed in our laboratory within one day by one technician. This seems to be a reasonable time effort for the assay of a tissue hormone in the picogram range.

The sensitivity of the enzymatic isotope assay is limited, as that of other methods, by the values for the blanks. They are equivalent to 0.7 ng histamine in the double isotope assay and to 0.1 ng in the single isotope assay (5). According to Bruce et al. (16) 0.2 ng histamine/ml plasma are detectable in a double isotope assay which is in accordance to the data of Beaven (5). Thus at present the sensitivity of the isotope assays is fully satisfactory for measuring histamine release, but it is not higher than that of our fluorometric assay. The specificity of the isotope assays depends on the high substrate specificity of histamine methyltransferase preparations which is generally true. The precision within-day was calculated by Beaven et al. (3) for a histamine quantity of 2.75 ng and was found to be 8% (n = 13). This precision is very similar to that measured in our fluorometric assay, and the accuracy seems to be established by comparing the results of the isotope assays with those of the bioassay and our fluorometric technique (Table I). Concerning the time needed for the assay it should be considered that it consists of an enzyme preparation, an incubation procedure (90 mins. incubation time), an extraction step and the time for liquid scintillation counting. This time largely equals that of the fluorometric assay.

Problems of Histamine Assays in Clinical Conditions: Hypotheses and Their Refutations by Experiments

In clinical conditions many problems appear which are unknown to basic research scientists who have developed a certain method. This is true both for the fluorometric and the enzymatic isotope assay for plasma histamine in human subjects.

(1) The fluorometric assay (Table II) is claimed to be more sensitive and specific, if incubations with o-phtaldialdehyde run at 0° C (ice water) instead of 21° C (room temperature) (17). For this reason we have performed our assay in the last time mostly at 0° C. But using the plasma substitute Haemaccel which is a gelatin preparation cross-linked by hexamethylene-diisocyanate we found two substances interfering with the fluorometric assay in this mixture

(18). Their fluorescence spectra (370/460 nm) were very similar to that of histamine (360/450 nm), but the luminescence intensity was much greater at 0° C than at 21° C. Furthermore their concentration in Haemaccel varied largely from batch to batch (Table III). The interference of Haemaccel fluorescence with histamine fluorescence could be avoided if the histamine release by Haemaccel in volunteers and patients was measured at 21° C using 0.05 percent o-phthaldialdehyde. The higher specificity of the fluorometric assay at 0° C (17), however, was no longer valid. Caution is always necessary when drugs or surgical treatments are applied.

The fluorometric assay has the advantage that its results can be examined easily for specificity by relatively simple tests. The formaldehyde test and the heating test are very useful in this respect (17). But the former does not work in canine gastric juice (19), giving false positive results, and the latter does not work when plasticizers are present in water or in the solvents prepared in plastic bottles, showing false negative results (Table III). The interfering substances in water (Table IV) or in the solvents (Table V) may elicit so much luminescence at the wave lengths of histamine as to account for about 4 ng

TABLE II

Problems of Histamine Assay in Clinical Conditions

(1) Fluorometric histamine assay

Hypothesis	Experimental refutation
1. The assay is more specific at 0° C than at 21° C	Not specific at 0° C when the plasma substitute Haemaccel was infused
2. The formaldehyde test is suitable for showing specificity	It does not work in canine gastric juice
3. The heating test is suitable for showing specificity	It does not work when plasticizers (phthalate esters) are present
4. Once specific, always specific	Not true in canine whole blood

TABLE III

Fluorescence Intensity in Haemaccel Extracts Treated Like Human Plasma at 2 Different Temperatures (T) and Concentrations of o-phthaldialdehyde (OPT)

Mean values ± S.D. from n bottles of Haemaccel. n.d. = not determined. For further conditions see (18).

Number of batches	n	Fluorescence intensity in ng histamine equivalent/ml Haemaccel®		
		T:0°C OPD:0.05%	T:21°C OPD:0.05%	T:21°C OPD:1%
2551	2	—	0	0
3000	10	18.1 ± 1.4	3.5 ± 0.5	12.6 ± 1.1
3123	2	31.2	–	–
3162	2	29.3	–	–
3212	3	24.1 ± 1.7	3.6 ± 0.4	13.5 ± 0.5
3214	2	15.3	2.5	10.3
V 139/III	2	7.3	0	2.2
V 143/II	4	16.0 ± 1.8	2.2 ± 0.2	9.4 ± 0.6
V 158/II	2	3.9	0	2.2
V 183/I	2	2.0	0	0.5

TABLE IV

Fluorescent Materials in Water Interfering with Histamine Assay

$\lambda(E) = 360$ nm, $\lambda(F) = 450$ nm, $\bar{x}$ from 2 tests/day. Water prepared and taken daily. 1 ng histamine (base)/ml 0.1 M HCl = 12 FU at 21° C.

Water preparation	Fluorescence units/2.5 ml water			
	April 1	April 2	April 5	April 6
Cuvette with air	3	4	1	0.5
Millipore® water	3.5	3.5	1	1
Deionized (central)	3	0.5	1.5	4
Deionized (peripheral)	4.5	3	3.5	4
Double distilled (direct)	4	3	4.5	2
Double distilled (tank)	25	14	12	18

TABLE V

Fluorescent Materials in Solutions Stored in Plastic Bottles Interfering with Histamine Assay

$\lambda(F) = 450$ nm. $\bar{x}$ from 2 tests/day. Solutions prepared in glass on May 24, 1976 and poured into different vials. 1 ng histamine (base)/ml 0.1 M HCl = 12 FU. The same bottles were used throughout the whole time.

Solution	Fluorescence units/2.5 ml solution at λ(E) 325 or 360 nm							
	May 24		May 26		May 31		June 6	
	325	360	325	360	325	360	325	360
Plastic bottles								
0.1 M HCl	12	11	10	11	12	12	9	10
1.0 M Na OH	28	11	28	10	26	10	27	10
3.0 M HCl	220	43	220	50	200	40	58	16
Glass bottles								
0.1 M HCl	4	7	5	5	4	6	4	3
1.0 M Na OH	5	4	4	5	4	2	3	2
3.0 M HCl	6	6	5	8	6	7	4	6

histamine/ml which is equivalent to plasma histamine concentrations during an anaphylactoid reaction (see below). Heating increases this fluorescence by a factor of 2-3. Thus histamine cannot be identified by the heating test in the presence of phthalate esters, and sometimes they are present everywhere (20). Only skillfully testing water, solvents, and glass-ware, and identifying the source of contamination can help.

The fluorometric assay, however, can also be impaired by endogenous substances in body fluids or tissues which may vary with diet, environmental conditions, genetic factors, etc. It should be expected that a method is specific if this once has been tested in a series of experiments (Table VI) (10). But this was not the case in canine blood when in another series of experiments in another city and with a time interval of several years solvents for anesthetics and several plasma substitutes were investigated in dogs (Table VII). In the first study the Dowex method (2, 4) for dog whole blood seemed as specific as the combined method (2, 4) whereas the classical extraction procedure according to Shore et al. (21) was unspecific (Table VI). In the second study more than 90 percent of the animals showed lower histamine values by the combined method than by the Dowex method (Table VII). The median was 8-times lower. There was some correlation between the values of the combined method

TABLE VI

Comparison of the Results of 3 Purification Procedures for the Histamine Assay in Dog's Whole Blood

Shore's method = butanol extraction, Dowex method = Dowex 50, combined method = Dowex 50 + butanol extraction. Analysis performed in June 1970. For further conditions see (21).

Animal No.	Purification procedure		Combined (3)
	Shore (1)	Dowex 50 (2)	
1	30	20	24
2	39	42	38
3	44	29	25
4	45	30	32
5	50	20	25
6	51	51	44
7	62	28	16
Median (lower and upper quartile)	45 (39–51)	29 (20–42)	25 (24–38)

TABLE VII

Histamine Equivalents (Dowex Method) and Histamine Concentrations (Combined Method) in Dog's Whole Blood

Series of experiments in 64 mongrel dogs (July 30–August 24, 1976), 2 values lost.

Method	Histamine equivalent values [ng/ml]		Rate of zero	Rate of correspondence
	Range	Median (quartiles 1–3)		
Dowex 50	5.2–124	12.9 (9.3–22.2)	0/62	4/62
Combined	0–60	1.7 (0.9–5.0)	8/62	4/62

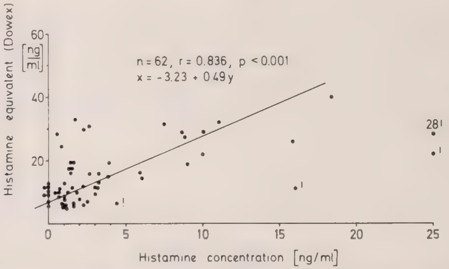

FIG. 1. *Correlation between histamine values obtained by the Dowex method and the combined method.* For definition of the two methods see text and Table VI. All values corrected for recovery (Shore 82%, Dowex 96%, combined method 68% on the average); ! = values in agreement.

and the Dowex method (Fig. 1), but the reliable value for the histamine content in canine whole blood was only 1.7 ng/ml which was much lower than the values in the literature. Was this value of 1.7 ng/ml really reliable? As Table VIII shows an exhaustive identification of histamine has been made to corroborate this finding. It seems, however, necessary for us to learn that in clinical conditions screening tests for the reliability of the methods used are mandatory.

(2) The enzymatic isotope assay (Table IX) is claimed to be specific because the histamine methyltransferase in this method is considered as absolutely specific for histamine. But this is not the case as Table X shows (22). Among the additional substrates of this enzyme also N^{α}-methylhistamine is found which has been detected in human urine (23). The pH-optimum and the K_m-value for this substrate and histamine methyltransferase from pig antrum (Fig. 2) (24) is quite reasonable for considering it as a serious candidate for interfering with the histamine assay.

TABLE VIII

Tests for Identification of Histamine in Dog Whole Blood and for Showing the Specificity of the Combined Method

For definition of the combined method see text and Table VI.

Analytical samples (n = 64):

1. Fluorescence spectra at 21° C
2. Heating test

Preparative samples (n = 3, 1 pool of n = 64)

3. Thin-layer chromatography on cellulose MN 300 in 5 solvent systems
4. Inactivation by purified histamine methyltransferase from guinea-pig brain and pig antrum (identical kinetics)
5. Degradation by purified diamine oxidase from pig kidney (identical kinetics)
6. Bioassay on isolated guinea-pig ileum, comparison of fluorometric results with those obtained by bioassay. pA_2-values with antazoline and mepyramine

TABLE IX

Problems of histamine assay in clinical conditions

(2) Enzymatic isotope assay.

Hypothesis	Doubts or refutations
1. The assay is specific because HMT has a high substrate specificity	There are some other substrates, too
2. The assay is specific for rat plasma	Fluorometry gives 10-times lower values
3. The assay is specific for human urine	Urinary analyses of patients with mastocytosis do not show elevated 24 hour histamine excretion in most of the cases
4. The assay is sensitive in all cases	Inhibitors of HMT are present in drug preparations (Haemaccel) or tissue

TABLE X

Acceptor Substrates of Histamine Methyltransferase from Pig Fundus Mucosa

Incubation conditions optimum for histamine (pH 7.4). Data obtained from Barth et al. (22, 24).

Substrates	Methylation [%] of substrate concentration [M]				
	10^{-6}	10^{-5}	10^{-4}	10^{-3}	10^{-2}
Histamine	24	64	96	53	32
N^{α}-Methylhistamine	0	5	12	18	16
4-Aminoethylthiomethyllymidazole	2	3	11	21	15
5-Methyl-4-aminoethylthiomethylimidazole	—	—	2	5	7

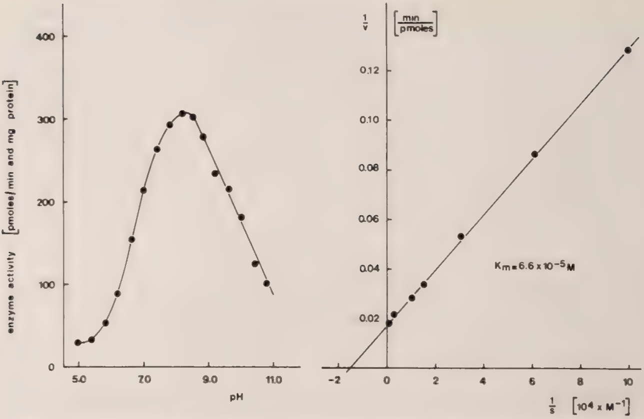

FIG 2. *Dependence of histamine methyltransferase activity on the pH-value and N^{τ}-methylhistamine concentration.* Mean values from 2-3 determinations. For further conditions see Barth et al. (24).

Furthermore, there are two conditions where the isotope assay shows higher histamine concentrations than the fluorometric assay or the bioassay (Table IX): 1) In rat plasma fluorometry gives values (8, 25) 10 times lower than those reported by Beaven et al (3). 2) Urinary analyses of 20 patients with mastocytosis did not show elevated 24 hour-histamine excretion in all but two cases if the combined method (Dowex 50 and butanol extraction) was used for separation of the amine and the determination of histamine then was performed by bioassay. We have talked with M. Beaven about this problem, and it seems very probable that problems in sample-taking were responsible for these discrepancies than rather substantial analytical differences (26). In this connection it must be admitted that the fluorometric assay even using the combined method (2, 4) can still not be used for histamine determination in human urine because it gives higher values than those being true histamine in the identification procedures listed up in Table VIII. We think, however, that at present it is one of the main advantages of our fluorometric set up including histamine methyltransferase and diamine oxidase that we can test the specificity and accuracy of our histamine assay in all conditions and that we can exclude those results under clinical circumstances which are not corroborated by various other techniques based on completely different principles, such as fluorometry, enzymatic analysis with and without isotopes (8), thin-layer chromatography and bioassay (1, 2, 4, 8, 10, 27–29).

Only in this way we have also detected clinical and laboratory conditions where both the sensitivity and the accuracy of the enzymatic isotope assays can be considerably impaired: Inhibitors of histamine methyltransferase were present in drug preparations, tissues or the reagents used for histamine assay

(Table IX). One example for this is again Haemaccel, a remarkable drug in histamine release studies since it also shows H_1-receptor antagonism on the isolated guinea-pig ileum (18): Haemaccel inhibits histamine methyltransferase strongly at low histamine concentrations as they are detected in human plasma, but enhances the enzymic activity at optimum histamine concentrations (about 10^{-4} M) (18). Endogenous inhibitors of histamine methyltransferase have been discussed by Kobayashi and Maudsley (30) and others (19, 24, 31). There was, however, a very interesting case of histamine methyltransferase inhibition which was observed during studies on histamine in duodenal ulcer disease (Table XI). Since in this disease a lower histamine content in gastric mucosa was measured than in control subjects (32) the possibility of interfering (fluorescing or quenching) substances occurring in the mucosa had to be excluded. Thus an identification of histamine in biopsy specimens was performed using spectra, heating test, bioassay, diamine oxidase and histamine methyltransferase. In all but one test system authentic histamine and the substance isolated from the biopsies were identical. But during incubation with histamine methyltransferase the disappearance of fluorescence was much slower with extracts from biopsies (only butanol extraction) rather than with authentic histamine indicating an inhibition of the enzyme by about 80 percent. Finally the inhibitor, however, was found in the extraction procedure since authentic histamine added to perchloric acid and treated like a biopsy showed the same slowing-down of the reaction velocity. Since inhibitors of histamine methyltransferase were even found in preparations of the radioactive cosubstrate S-adenosylmethionine (33), one should never exclude the possibility, that the sensitivity or even, the accuracy of the enzymatic isotope assays can be impaired considerably under various conditions.

Plasma Histamine Concentrations and Clinical Symptoms Following Administration of Exogenous Histamine

Plasma histamine determinations following application of exogenous histamine in human subjects have been reported only for the fluorometric assay (7,

TABLE XI

Inactivation of Authentic Histamine and the Substance Isolated from Human Corpus Mucosa by Pig Antrum Histamine Methyltransferase

Fluorometric histamine assay in the biopsy samples (mean of 5 specimen) after butanol extraction according to Shore et al. (21). Preparation of same quantity of authentic histamine in 0.1 M HCl. Neutralisation of the tissue extract and the solution containing authentic histamine. Incubation of both mixtures with histamine methyltransferase according to (8). Extraction of the residual histamine and fluorometric assay according to Shore et al. (21), but using 0.05 o-phthaldialdehyde.

Incubation time [min]	Authentic histamine [FU]		Bioasay specimen [FU]	
	Sample 1	Sample 2	Sample 1	Sample 2
0	56.5	40	55.0	45
15	18.0	10	43.0	29
30	8.5	2	36.0	16
60	1.8	1	28.5	9
120	0	0	17.0	2
180	—	2	—	0

34). During intravenous infusion of clinically relevant doses of histamine (i.e., those used for the histamine-infusion test for stimulating gastric acid secretion) there was a step-wise increase of plasma histamine levels (Fig. 3). They fell down to approximately basal levels within 15 mins. after stopping the infusion. Gastric acid secretion was observed at plasma histamine levels above 1 ng/ml, tachycardia at those above 4 ng/ml. These reactions to histamine could not be blocked by the H_1-receptor antagonist antazoline.

Intravenous injection of a small dose of histamine into 40 human volunteers (600 ng/kg) was performed during a controlled clinical trial on histamine release by two preparations of the plasma substitute Haemaccel (Behringwerke, Marburg, West Germany). This trial has already been mentioned in this communication, in the section where the precision of the fluorometric assay has been tested by quality control. Now the maximum increases of the

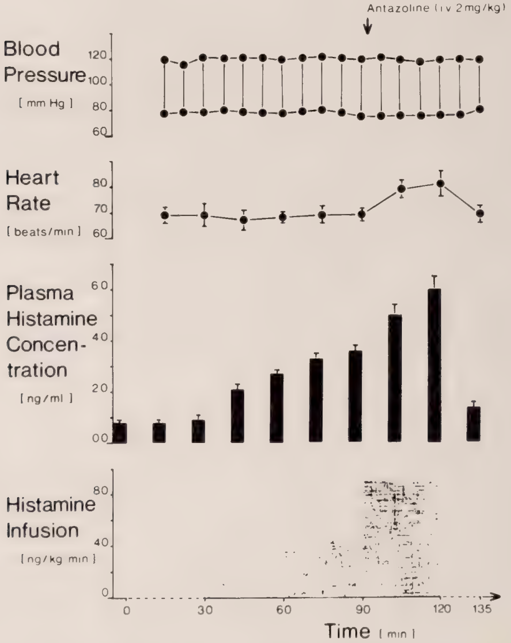

FIG. 3. *Plasma histamine concentration, heart rate and blood pressure after intravenous infusion of increasing doses of histamine.* Mean values ± S.E.M. from 3 test persons. For further conditions see (7, 34).

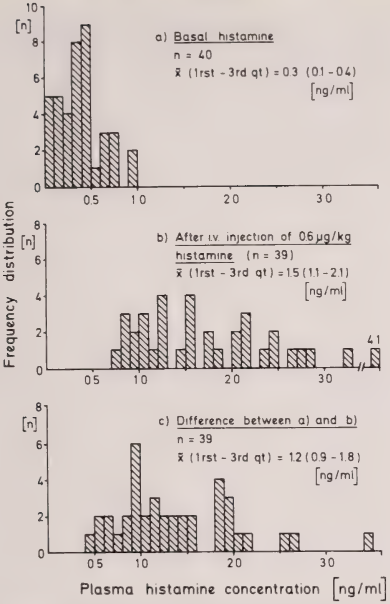

FIG. 4. *Plasma histamine concentrations in human volunteers before and after injection of histamine in a controlled clinical trial on histamine release.* Basal histamine levels as means from two determinations, those after histamine injection as single values (maximum increase in plasma histamine concentration). For further conditions see text and Table XII.

plasma histamine level are shown after the injection of histamine as well as the clinical reactions of the volunteers to this application (Fig. 4, Table XII). The range of the maximum increases (0.4–3.3 ng/ml) was considerably large, but the augmentation could be measured in all volunteers tested. The highest histamine levels were determined always 1 min. after injection, then clearance curves were obtained with a half-life of about 2 mins. Changes in pulse rate were observed only in 75 percent of the individuals after histamine injection, changes in blood pressure (hypotension!) occurred in none of them. Also none of clinical symptoms showed an incidence of 100 percent. Thus the determination of plasma histamine levels was expected to be the most sensitive test for demonstrating histamine release in man under various clinical conditions.

The doses for histamine infusion and injection were chosen in order to mimic the clinical syndrome of a small, but significant histamine release which occurs much more often than the life-threatening anaphylactoid reactions (see below).

TABLE XII

Incidence of Increase in Plasma Histamine Levels, Changes in Pulse Rate and Blood Pressure and Clinical Symptoms after i.v. Injection of 0.6 μg/kg Histamine in Man

40 test persons (32 male, 8 female, age 21–37). Increase in pulse rate 10 (0–20) beats/min (median, 1st–3rd quartiles). 1 plasma was lost.

Parameters or symptoms	Incidence
Increase in plasma histamine (>0.4 ng/ml)	39/39
Increase in pulse rate (>5 beats/min)	30/40
Changes in blood pressure (>5 mm Hg)	0/40
Flush	36/40
Metallic taste	32/40
Headache	21/40

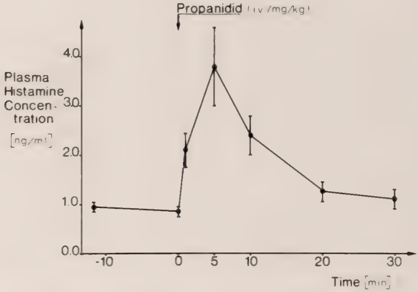

FIG. 5. *Plasma histamine concentrations in human subjects after intravenous injection of propanidid (Epontol®).* Mean values ± S.E.M. from 12 test persons. For further conditions see (34).

The small histamine release, however, by no means is negligible since it impairs cardiac function (35) and induces formation of stress ulcers (36, 37).

Evidence for Histamine Release in Man as a Significant Pathophysiological Principle

Histamine release in man under clinical conditions was first demonstrated in volunteers and patients suffering from severe incidents to the anaesthetic drug propanidid (Epontol®) (38–40).

(1) A reliable plasma histamine assay was applied to this problem. In all test persons of one series an increase of plasma histamine levels up to 3 ng/ml was determined (Fig. 5). In three other volunteers, and especially in one patient with high basal histamine concentrations (4, 34, 41, 42) a considerable to excessive augmentation of plasma histamine was observed (Fig. 6). The kinetics of the plasma histamine levels in all cases corresponded largely to a Bateman function which should be expected in the case of histamine release (7, 8, 34).

(2) The changes in plasma histamine levels after injection of the drug were accompanied by clinical symptoms and biological reactions which with respect to intensity and time course corresponded to the alterations in plasma histamine concentration (Fig. 6 and 7). Furthermore they corresponded at lower plasma histamine levels (up to 6 ng/ml) to those produced by administration of exogenous histamine in test persons, at higher plasma histamine levels (10 ng/ml and more) to those recorded in dogs following application of relatively large doses of exogenous histamine (6 μg/kg i.v. (8, 10, 43, 44)). Dogs were chosen since they are comparably as sensitive to histamine as human beings

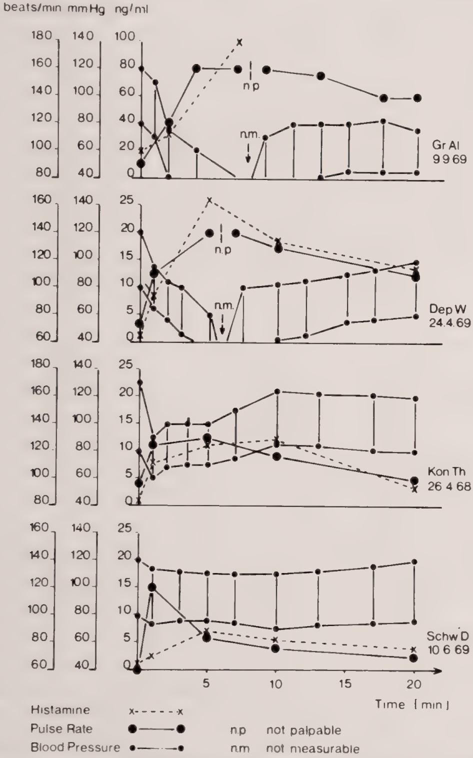

FIG. 6. *Correlation between plasma histamine concentration, pulse rate and blood pressure in four cases of anaphylactoid and "allergic" reactions to propanidid (Epontol®).* Values from single determinations. For further conditions see (34).

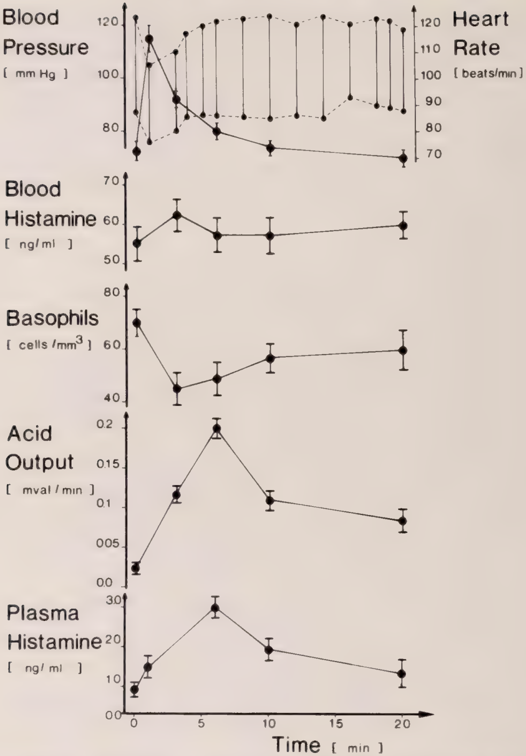

FIG. 7. *Histamine concentration in plasma and whole blood, gastric acid secretion, blood pressure and heart rate after intravenous injection of propanidid (Epontol®).* Mean values ± S.E.M. from 5 test persons.——heart rate, ... blood pressure. For further conditions see (34).

and since high doses of histamine could not be administered in volunteers for ethical reasons.

(3) The combination of an H_1- and an H_2-receptor antagonist was not available for injection in man at the time of these investigations on propanidid. This combination, however, has been tested using another clinically significant histamine releaser, Haemaccel®, in dogs and human subjects (44a). As later on will be shown, the combination of dimethpyrinden maleate and cimetidine completely blocked the clinical symptoms of an anaphylactoid reaction both in the animals and volunteers though histamine release could be shown in them by histamine determination in blood and plasma.

These three findings demonstrate definitely that histamine release in clinical conditions has a pathophysiological significance. Histamine no longer has to be suspected as a dubious substance, but is well established now as a biological, not only as a pharmacological principle.

Histamine Release in Human Subjects by Drugs Used in Anaesthesia and Surgery (a Survey)

Anaesthetic drugs, muscle relaxants, drugs for premedication in anaesthesia, protease inhibitors and plasma substitutes have been investigated for their histamine releasing activity in man using clinical doses and the clinical route of application. Table XIII shows a survey of these findings.

Among the *anaesthetics and hypnotics* in our series only etomidate was found free of histamine release up to now (37, 45). Propanidid and althesin were the strongest histamine releasers (34, 41, 42, 45), but thiopentone and methohexitone were also effective (34, 37, 45). In clinical incidents occurring as anaphylactoid reactions or shock histamine release could be demonstrated only in the case of propanidid (4 subjects) (34) and althesin (1 subject) (45). It is, however, worthwhile to consider that severe reactions in clinical conditions occur not every day and are relatively rare when thiopentone and methohexitone are applied. Thus we had no chance to measure plasma histamine levels in such events. Histamine release with plasma histamine levels of about 3 ng/ml which has been observed with the latter two drugs may have effects on

TABLE XIII

Histamine Release in Man by Drugs used in Anesthesia and Surgery

Substances	Number of test persons	Dose [mg/kg i.v.]	Result of testing
Anesthetics and hypnotics:			
Propanidid	24	5–7	+
Thiopentone	15	5	+
Methohexitone	10	2.5	+
Althesin	8	0.075	+
Flinitrazepam	10	0.02	+
Etomidate	33	0.2	–
Muscle relaxants:			
Succinylcholine	8	0.7	+
Alloferin	8	0.15	+
Pancuronium	8	0.1	+
Premedication:			
Atropine	36	0.01	+
Promethazine	10	0.4	–
Dimethpyrindene	8	0.04	–
Protease inhibitors:			
Aprotinin	10	6000 E/kg	–
Plasma substitutes:			
Haemaccel	80	6 ml/kg	+
Oxypolygelatin	10	6 ml/kg	+
Dextran 60	35	6 ml/kg	+
Hydroxyethyl starch	20	6 ml/kg	+

cardiac function (35). But there are no physical tests in clinical situations which have been applied to studies on histamine release up to now. It seems interesting to note that also flinitrazepam which is a diazepam derivative releases histamine in test persons. One of the common features of all anesthetic drugs investigated is their lipophilic property. As solvents therefore detergents have to be used which were shown to be excellent histamine releasers in dogs (46). Propanidid and althesin, for instance, which do not show any structural similarity both release histamine in man and dogs. Their solubilizer is cremophor El which is a strong histamine releaser in dogs and cats (1, 43, 46, 47). Since in man cremophor El showed only symptoms of histamine release when it was intradermally injected (48), but not following intravenous application, it was concluded that the combination of anesthetic drug plus nonionic detergent may be responsible for histamine release in man (1, 34, 45).

Muscle relaxants have been considered for many years to be histamine releasers in man, but for the first time it could be demonstrated that they liberate histamine under clinical conditions (49). Muscle relaxants in human subjects are never administered without anesthesia, therefore in none of the case reports in the literature can it be excluded that anaphylactoid reactions to the muscle relaxants were the result of the anesthetic drug or at least due to the combination of the narcotics and the relaxant. We have used etomidate in our studies with muscle relaxants which did not release histamine in our test persons when given alone. It seems reasonable to conclude that histamine release by etomidate plus suxamethonium, alloferine and pancuronium bromide was caused by the relaxants, but even with etomidate we had some minor doubts (49). In our studies it was especially remarkable that pancuronium was as effective in releasing histamine as alloferine and only slightly less potent as suxamethonium. Animal experiments sometimes may not reflect the clinical situation.

This statement was even more true for drugs used as *premedication* before introduction of anesthesia and before starting surgical treatment. Antihistaminics (H_1- receptor antagonists and biminamide) were shown to be very potent histamine liberators in animals (10, 43, 50–52). But following intravenous or oral application in man in doses used for premedication they did not elevate plasma histamine concentrations in any test person. Atropine, however, was effective in 6 of 36 individuals investigated (37).

Aprotinin (Trasylol) is a basic polypeptide which should be expected to release histamine. Clinical observations of anaphylactoid reactions to this drug in patients with chronic pancreatitis seemed to confirm this assumption. To our surprise, however, even the relatively large dose of 6000 U/kg i.v. did not elevate the plasma histamine concentration in any of the volunteers tested.

Plasma substitutes all were shown to release histamine in man. This effect will be discussed in detail in the following section, since new aspects concerning histamine release in man by drugs were detected applying these mixtures.

Using the fluorometric assay for plasma histamine determination Meyer-Burgdorff et al. (53) confirmed our findings concerning histamine release in man by propanidid. No increase in plasma histamine concentrations, however, could be detected during anaesthesia with ketamine, halothane or nitrous oxide (53).

Anaphylactoid Reactions and Histamine Release in Man and Dog by Plasma Substitutes

Histamine release in animals by plasma substitutes is known for many years (for a survey see 54, 55, 56), but the literature is full of inaccurate data due to unreliable methods for measuring blood and plasma histamine. Thus for instance dextran has been described to be a histamine releaser in dogs (57), but using the Shore's method for histamine determination in plasma values were obtained which are too high by several hundred percents. No histamine release at all (58) or only a very small, clinically insignificant histamine release in few of the animals (see below, Table XX) was detected when the fluorometric Dowex method or the combined method were used for measuring histamine in canine blood.

With the aid of reliable methods for measuring histamine release (see introduction) considerable species differences have been established concerning histamine liberation by plasma substitutes. Their relevance for human subjects is not clear. (1) *Dextran* in preparations which are clinically administered releases histamine in rats (59) and rabbits (60), but not in dogs (58) and pigs (27). (2) *Gelatin* preparations increase whole-blood histamine concentrations in dogs (88) and plasma histamine concentrations in monkeys (37), but do not release histamine in guinea-pigs, rats (61, 62) and rabbits (Lorenz, unpublished data). (3) *Hydroxyethyl starch* elevates blood histamine levels in dogs, but only with a low incidence and only up to concentrations which do not influence the blood pressure (Table XX). In rats, however, it is without effect (63). (4) Human serum albumin releases histamine in dogs (64), but there is nothing known about its effect in other species.

Adverse reactions to plasma substitutes in man have been reported in many countries (for a survey see Lorenz et al. (11)). They occur as anaphylactoid reactions to human serum albumin (65), to dextrans (66, 67), oxypolygelatin (67, 68), gelatin crosslinked by hexamethylene diisocyanate (11, 69) and gelatin crosslinked by succinic acid anhydrate (70). In the last time they were observed also following application of hydroxyethyl starch (67, 71) though the incidence of reactions to this drug at present seems to be slightly less than that to other artificial colloids (69). The smallest incidence of anaphylactoid reactions was observed after infusion of human serum albumin, but this plasma expander is very expensive.

The question whether anaphylactoid reactions in man to plasma substitutes are due to histamine release has been tested with several of these preparations using our fluorometric plasma histamine assay (11, 15, 37, 40, 49, 72–74). In test persons all of them released histamine in small amounts with a more or less high incidence. In severe anaphylactoid reactions, however, only gelatin crosslinked by hexamethylene diisocyanate (Haemaccel®) elevated the plasma

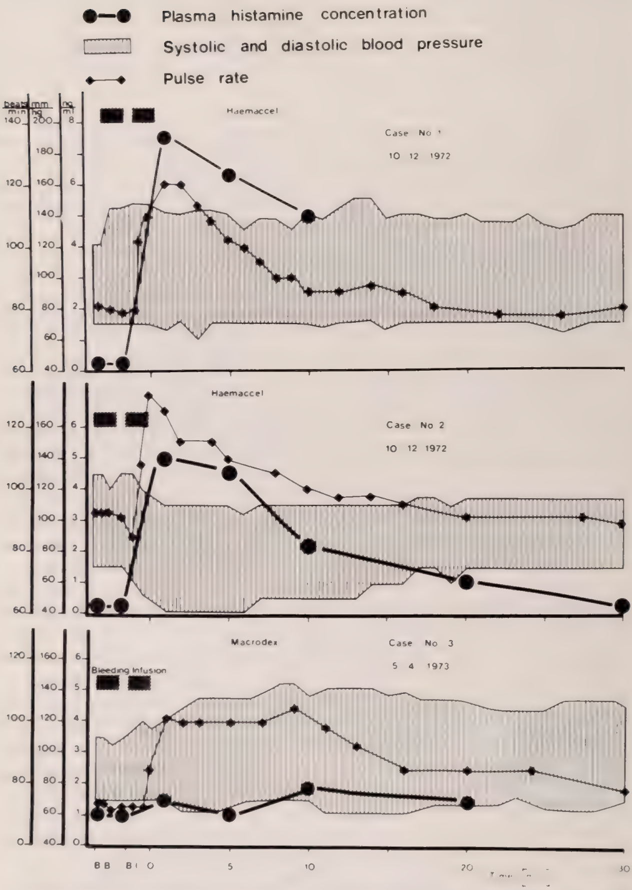

FIG. 8. *Correlation between plasma histamine concentration, pulse rate and blood pressure in three cases of anaphylactoid reactions to Haemaccel and dextran-60 (Macrodex).* Single values from each of the test persons. B.B. = before bleeding, B.I. = before infusion. For further conditions see (11).

histamine concentration to such an extent that this could explain completely the severity of the reaction to this drug (11) (Fig. 8). But even two life-threatening reactions to dextran (11) (Fig. 8) were not accompanied by a significant histamine release. These findings prompted us to perform several controlled trials in human subjects and in dogs (Table XIV).

(1) *In trial No. 1* infusion of Haemaccel and injection of exogenous histamine were tested in the same subjects. Following application of the two drugs into the right cubital vein a monoexponential clearance curve for the plasma histamine level was obtained in blood taken from the left cubital vein. Thus earlier results on histamine release in man by Haemaccel could be confirmed (11). The increase in plasma histamine concentrations following Haemaccel infusion, however, did not correspond to the production of all clinical ("allergic") symptoms of the drug. There were three anaphylactoid reactions which could be specifically predicted by the determination of plasma histamine (Table XV), but the efficiency of the plasma histamine assay for predicting wheals was only 63% which was only slightly better than flipping a coin (9). Studies of Kaplan (75) who used the enzymatic isotope assay for plasma histamine have confirmed our finding. He collected the blister fluid and demonstrated local histamine release by measuring histamine in it, but he was unable to show elevated plasma histamine levels under these circumstances. These findings are by no means arguments against histamine release being the main cause for anaphylactoid reactions by Haemaccel. If the effects of exogenous histamine and Haemaccel in the three test persons with anaphylactoid reactions were compared a reasonable correspondence of these effects was obtained (Table XVI). Pharmacokinetics, of course, have to be considered in this comparison: 1) From experiments in dogs it is known that Haemaccel releases histamine mainly from the skin of the upper half of the body and from the liver (10). 2) Histamine release is a more long-lasting process than intravenous injection of histamine which could be demonstrated very nicely in dogs (8). *Thus in conclusion the increase of plasma histamine levels corresponds to systemic clinical symptoms and biological reactions, but not to local responses to a certain drug or treatment.*

(2) *In trial No. 2* (Table XIV) all four plasma substitutes released histamine in the test persons, but the incidence was relatively low (Table XVII). Each case of histamine liberation, however, was confirmed by measuring a clearance curve for plasma histamine levels and by a maximum increase to values above 1 ng/ml (for definition of histamine release see (1, 10)). With the exception of an anaphylactoid reaction to Haemaccel, however, there was no correspondence between the increase in plasma histamine levels and the clinical symptoms (Table XVII, XVIII). As far as Haemaccel is concerned this result in trial No. 2 confirms those of trial No. 1 indicating that increase in plasma histamine levels above 2.5 ng/ml is associated with symptoms of an anaphylactoid reaction.

The generalized urticaria to oxypolygelatin, especially in the test person No 17, which was associated with some discomfort has to be considered as an

TABLE XIV

Controlled Trials in Human Subjects and in Dogs on Anaphylactoid Reactions and Histamine Release by Plasma Substitutes

The samples are given in number of test groups × number of individuals.

No.	Design	Questions	Conditions
1	Controlled trial in test persons using Haemaccel and exogenous histamine	(1) Does the increase in plasma histamine levels correspond to clinical symptoms and biological reactions? (2) Does exogenous histamine produce similar plasma levels and similar biological reactions as gelatin infusion in the same subjects?	1 × 40 individuals, Haemaccel (4 batches randomized) 7 ml/kg (2 ml/(kg × min)) i.v.; histamine 600 ng/kg i.v.; procedure and methods according to (11); further details see text in section 1 and 3.
2	Controlled randomized trial in test persons using four commonly applied plasma substitutes	(1) Do all four plasma substitutes (polyurea gelatin = Haemaccel, dextran-60 = Macrodex, hydroxyethylstarch 400 = Plasmasteril, oxypolygelatin = Gelifundol S) release histamine in man when tested at the same time? (2) Does the increase in plasma histamine levels correspond to clinical symptoms and biological reactions?	4 × 10 individuals, all plasma substitutes (1 batch only) 7 ml/kg (2 ml/(kg × min)) i.v.; procedure and methods according to (11)
3	Controlled randomized trial in mongrel dogs using five commonly applied plasma substitutes and phosphatidyl serine	(1) Do all five plasma substitutes (Haemaccel, Macrodex, Plasmasteril, Gelifundol and gelatin crosslinked by succinic acid anhydride = Neoplasmagel) and phosphatidyl serine produce anaphylactoid reactions in dogs? (2) Do all of them release histamine? (3) Does the increase in blood histamine levels correspond to biological reactions (clinical symptoms, pathology, blood pressure response?) (4) Does phosphatidyl serine enhance histamine release in dogs as in rats?	8 × 8 animals, all plasma substitutes (2 batches randomized) 20 ml/kg (6–7 ml/(kg × min)) i.v., phosphatidyl serine 100 μg/kg i.v., procedure according to (10), combined method for blood histamine, quality control using pooled blood from all animals before and after treatment
4	Controlled randomized trial in mongrel dogs using Haemaccel and the combination of an H_1- and H_2-receptor antagonist	(1) Does the combination of an H_1- and H_2-receptor antagonist prevent anaphylactoid reactions in dogs? (2) Does this treatment influence histamine release? (3) Does this treatment show side-effects when no histamine release is involved?	2 × 20 animals, Haemaccel (4 batches randomized, two with low and high incidence of reactions, respectively) 20 ml/kg (6–7 ml/(kg × min)) i.v., procedure according to (10), combined method for blood histamine. Quality control as in No. 3.

TABLE XV

Efficiency of Plasma Histamine Assay for Predicting Anaphylactoid Reactions and Wheals ("Allergic Reactions") Following Haemaccel Infusion

PV = predictive value, HL = histamine level. Anaphylactoid reaction = generalized urticaria, respiratory distress, tachycardia, hypotension. As a fragment of this reaction at least generalized urticaria and personal discomfort has to be established (44a). For further conditions see Table XIV, trial No 1.

a) *Anaphylactoid reactions*

	Increased HL [>2.5 ng/ml]	No increased HL	Totals
Anaphylactoid reaction	3	0	3
No anaphylactoid reaction	0	37	37
Totals	3	37	40

—PV positive = 100%
—PV negative = 100%
—Incidence = 8%
—Efficiency = 100%

b) *Wheals ("allergic reactions")*

	Increased HL	No increased HL	Totals
Wheals	9	12	21
No wheals	3	16	19
Totals	12	28	40

—PV positive = 75%
—PV negative = 57%
—Incidence = 53%
—Efficiency = 63%

anaphylactoid reaction according to our definition (Table XV). In this case no significant histamine release into the plasma has been observed.

(3) In order to find some explanations for these contradictory results we performed *trial No 3* (Table XIV) in dogs. Higher doses of the plasma substitutes than in test persons could be administered into the animals. The speed of infusion was rather high, but was always standardized and corresponded to that used in some emergency situations in man. Of course, this infusion speed was elected in order to produce a higher incidence of reactions both in test persons and in animals. But since in normal clinical conditions the incidence of anaphylactoid reactions to plasma substitutes may be in the range of 1:1000 - 1:10000, there would be no chance to study them in a practicable number of individuals. As Table XIX demonstrates anaphylactoid reactions occurred after infusion of all five plasma substitutes, but the incidence was different. Haemaccel was effective in all animals, dextran in two, hydroxyethyl starch in one (very strong reaction!). Phosphatidyl serine did not significantly increase the incidence of these reactions. As Table XX demonstrates the anaphylactoid reactions following Haemaccel infusion were all accompanied by a strong histamine release whereas none of the reactions to the other drugs

TABLE XVI

Comparison of the Effects of Exogenous Histamine and Haemaccel in Three Test Persons with Anaphylactoid Reactions

Increase in plasma histamine is given as ng/ml. PR = Pulse rate (beats/min), BP = blood pressure (mm Hg). No hypotension was observed. Note the longer duration of symptoms following Haemaccel than after histamine injection which corresponded to a more longlasting elevation of plasma histamine concentrations. For further conditions see Table XIV, trial No 1.

Test person No	Exogenous histamine		Haemaccel	
	Symptoms and reactions	ng/ml	Symptoms and reactions	ng/ml
21	Metallic taste	3.2	Metallic taste	4.6
	Flush, tears		Flush, tears	
	— — — — —		Sneezing, coughing, respiratory distress, wheals, blepharoedema	
	Stop after 3 mins.		Stop after 15 mins.	
	PR + 27		PR + 60	
	BP + 10		BP + 15	
33	Flush	2.2	Flush	3.0
	Slight respiratory distress		Respiratory distress	
	Metalic taste		—	
	— —		Sneezing, wheals	
	Stop after 5 mins.		Stop after 18 mins.	
	PR 0		PR + 13	
	BP + 10		BP + 10	
6	Headache	2.0	Headache	2.7
	Narrowness in throat		Narrowness in throat	
	Metallic taste, flush		flush	
	—		wheals	
	Stop after 8 mins.		Stop after 15 mins.	
	PR + 16		PR 0	
	BP + 5		BP + 8	

TABLE XVII

"Allergic" and Anaphylactoid Reactions and Histamine Release in Test Persons Following Infusion of Plasma Substitutes

n = number of subjects showing the attribute in a sample of 10. As the total 40 individuals were investigated. With exception of case * no correspondence between skin reaction and histamine release was observed. This means that subjects with skin reactions showed no histamine release and subjects with histamine release showed no skin reactions. For definition of anaphylactoid reactions see Table XV and XVIII, for further conditions see Table XIV, trial 2.

Plasma substitute	Skin reactions [n]	Increase in plasma histamine [n]	
		<2.5 ng/ml	> 2.5 ng/ml
Haemaccel	4	1	1*
Macrodex	0	1	1
Plasmasteril	0	2	0
Gelifundol S	3	1	0

TABLE XVIII

"Allergic" and Anaphylactoid Reactions in Test Persons Following Infusion of Plasma Substitutes

Cases No. 17 and 38 were defined as anaphylactoid reactions in the series of 40 test persons. For definition see Table XV, for further conditions Table XIV, trial No 2. Note the very low plasma histamine concentrations before infusion of the drugs which were all below 100 pg/ml.

Test person No	Plasma substitute	Clinical observations	Plasma histamine concentration (ng/ml)	
			Before infusion	After infusion
9	Haemaccel	Slight flush for 2 mins. during infusion	0	0
17	Gelifundol S	Flush, generalized urticaria, but no tachycardia, no respiratory distress	0	0.3
20	Gelifundol S	One wheal on the neck	0	0
29	Haemaccel	Slight flush for 2 mins. during infusion	0	0
36	Gelifundol S	6 mins. after infusion one wheal on the forehead, then several wheals and erythema on the face	0	0
38	Haemaccel	Sneezing at the end of infusion, flush, 5 mins. later respiratory distress, tachycardia (88 → 112 beats/min). No therapy.	0	4.2
39	Haemaccel	One wheal on the chest	0	0.3

TABLE XIX

Anaphylactoid Reactions to Plasma Substitutes and Phosphatidyl Serine in Anaesthesized Dogs

Definition of anaphylactoid reactions by arterial hypotension of the delayed type which lasted for more than 5 mins and amounted to more than 25 mm Hg. Clinical symptoms, such as oedema at the nose or hyperventilation and respiratory distress, macroscopical and microscopical pathology showing liver outflow block, lung oedema and swelling of the kidneys were considered additionally. Cardiac necroses were not seen in any case. The single data of each animal are presented (maximum extent and time of hypotension (systolic pressure)), time = mins after stopping infusion. PS = phosphatidyl serine, MKD = dextran-60, HÄS = hydroxyethyl starch, HÄM = Haemaccel, GEL = oxypolygelatin, NPG = gelatin cross-linked by succinic acid anhydride. Note that PS caused only a short-lasting hypotension (no anaphylactoid reaction). For further conditions see Table XIV, trial No 3.

Rank	Hypotension in mm Hg (time in mins.)							
	PS	MKD	MKD + PS	HÄS	HÄM	HÄS + PS	GEL	NPG
1	10 (0.2)	0	0	0	80 (0)	0	0	0
2	10 (0.2)	0	0	0	85 (2)	0	0	0
3	15 (0.2)	0	0	0	90 (0)	0	0	0
4	20 (0.2)	0	0	0	90 (1)	0	0	0
5	22 (0.2)	0	0	0	90 (2)	0	0	0
6	25 (0.2)	0	0	0	95 (2)	0	10 (4)	10 (14)
7	30 (0.2)	10 (6)	0	6 (7)	110 (2)	0	35 (20)	14 (18)
8	40 (0.2)	55 (1)	30 (1)	140 (8)	140 (3)	6 (8)	60 (2)	115 (2)
Median	21	0	0	0	90	0	0	0
(1st–3rd quartiles)	(10–30)	(0–10)	(0–0)	(0–6)	(85–110)	(0–0)	(0–35)	(0–14)

TABLE XX

Histamine Release Following Administration of Plasma Substitutes and Phosphatidyl Serine in Dogs

Definition of histamine release according to (10): Increase of histamine levels up to more than 1 ng/ml plasma or blood and demonstration of a clearance curve. The single data of each animal are presented (maximum extent and time of increase in blood histamine). For pre-infusion data of the dogs see Table VII and Fig. 1. For further conditions see Table XIV, trial No 3 and Table XIX. The ranking numbers in Table XIX and XX are not identical. Case No 8 of phosphatidyl serine was no histamine release according to our criteria (10).

Rank	Increase in histamine concentration [ng/ml] (time in mins.)							
	PS	MKD	MKD + PS	HAS	HAM	HAS + PS	GEL	NPG
1	0	0	0	0	12.0 (1)	0	0	0
2	0	0	0	0	26.7 (1)	0	0	0
3	0	0	0	0	30.0 (1)	0	0	0
4	0	0	0	0	30.0 (1)	0	0	0
5	0	0	0	0	39.0 (1)	0	0	0
6	0	0	0	0	78.4 (5)	1.5 (5)	0	0
7	0	0	1.1 (1)	1.8 (5)	85.5 (1)	3.9 (1)	2.4 (8)	2.1 (5)
8	1.7 (20)	0	3.0 (5)	5.4 (5)	131.0 (1)	6.0 (1)	3.5 (1)	2.9 (1)
Median	0	0	0	0	34.5	0	0	0
(1rst–3rd quartiles)	(0–0)	(0–0)	(0–1.1)	(0–1.8)	(26.7–85.5)	(0–3.9)	(0–2.4)	(0–2.1)

TABLE XXI

Hypotension and Histamine Release in Dogs by Haemaccel Following Administration of an H_1- and H_2-Receptor Antagonist

Single values and medians from 40 animals. LTB = 2 low toxicity batches, HTB = 2 high toxicity batches (See Table XIV). Dimethpyrindene (H_1-antagonist) 1 mg/kg i.v., cimetidine (H_2-antagonist) 5 mg/kg i.v., different ranking for hypotension and histamine release. Significance for differences in hypotension between HTB + NaCl and HTB + antagonist $p < 0.01$ (Mann-Whitney test). For further conditions see Table XIV, trial 4.

Rank	0.9% NaCl				H_1- and H_2-receptor antagonist			
	Hypotension [mm Hg]		Increase in histamine [ng/ml blood]		Hypotension [mm Hg]		Increase in histamine [ng/ml blood]	
	LTB	HTB	LTB	HTB	LTB	HTB	LTB	HTB
1	0	0	0	5.3	0	0	0	0
2	0	30	0	10.1	0	0	0	1.2
3	0	35	0	21.3	0	0	0	2.9
4	0	60	0	37.5	0	0	0	8.4
5	0	110	0	42.5	0	0	0	19.6
6	0	120	0	55.2	0	0	0	22.7
7	0	140	0	69.4	0	0	0	48.7
8	0	150	0	72.0	0	30	0.7	52.2
9	0	170	0	107.5	0	30	1.1	62.2
10	0	—	0	—	—	40	—	91.3
11	40	—	1.9	—	—	50	—	113.7
Median	0	110	0	42.5	0	0	0	22.7
(1st–3rd quartile)	(0–0)	(30–150)	(0–0)	(10.1–72.0)	(0–0)	(0–30)	(0–0.7)	(2.9–62.2)

showed any significant relation to histamine release. The numbers in Table XX are listed in a ranking order which does not correspond to that in Table XIX. Thus absolutely no histamine release could be shown in the dog reacting to hydroxyethyl starch although macroscopical and microscopical pathology showed no other findings than those expected in an anaphylactoid reaction. From the results in trial No 3 it must be concluded that as in the case of dextran in man also in dogs severe anaphylactoid reactions can occur without any histamine release into the plasma. Since very low histamine concentrations can be measured in plasma today and only very low doses of exogenous histamine are necessary to be demonstrated in plasma (this paper) the most likely explanation for our finding is that other mediators than histamine cause the clinical symptoms and biological reactions to these drugs and that other mechanisms than those which include histamine release are involved in these anaphylactoid reactions. Thus for instance IgE and anaphylatoxins may not play a significant role in this kind of a "drug allergy". Other mediators which this kind of a "drug allergy". Other mediators which have to be considered are the plasma kinins, prostaglandins and slow-reacting substance A.

(4) In order to complete the evidence that Haemaccel elicited anaphylactoid reactions predominantly by histamine release and that *no other mediator* of inflammatory processes was significantly involved in the clinical syndrome we attempted to prevent these reactions by administering the combination of an H_1- and H_2-receptor antagonist in dogs (*trial No 4*) (Table XIV). Four different batches of Haemaccel were used: two which had been shown in pilot studies to produce a low incidence of anaphylactoid responses (LTB) and two afflicted with a high incidence (HTB). The combination of the two antihistaminics in the doses applied was chosen, since in prior investigations this had been found optimum (43, 47, 52, 76, 77) for several reasons, mainly because of its strong effects against histamine and its high specificity. As Table XXI shows the two

TABLE XXII

Anaphylactoid Reactions and Histamine Release Following Infusion of Plasma Substitutes in Human Subjects and Animals

Gelatin cross-linked by urea = Haemaccel, gelatin cross-linked by glyoxal = Gelifundol S, for further explanations see Table XIV. Dextran 75 = Salvia (Boehringer). + = positive result, – = negative result, n.t. = not tested.

Plasma substitute	Anaphylactoid reactions observed in clinics	Histamine release in			Histamine release roughly in agreement to symptoms
		Animals	Test persons	Clinical incidents	
Gelatin					
cross-linked by urea	+	Dog, monkey	+	+	+
cross-linked by glyoxal	+	Dog	+	–	–
cross-linked by succinic acid anhydride	+	Dog	n.t.	n.t.	–
Dextran					
Dextran-75	+	Rat	+	n.t.	n.t.
Dextran-60	+	Rat	+	–	–
Dextran-40	+	Rat	+	n.t.	n.t.
Hydroxyethyl starch					
HES-400	+	Dog	+	n.t.	–
Albumin	+	Dog	n.t.	n.t.	n.t.

histamine receptor antagonists prevented the anaphylactoid reactions induced by the two "toxic" batches completely, they did not significantly influence the histamine release elicited by them and they did not show any side-effects when no histamine release occurred following infusion of the two "non-toxic" batches.

For this reason a randomized controlled single-blind trial in 50 volunteers was performed to test whether dimethpyrindene (0.1 mg/kg) (H_1-blocker) plus cimetidine (10 mg/kg) (H_2-blocker) could prevent anaphylactoid or allergoid reactions following Haemaccel infusion. In the control group 6 anaphylactoid and 9 allergoid reactions were observed, in the $H_1 + H_2$-group, however, *none* of those reactions (44a).

Knowledge available from the literature as well as our own studies and clinical trials prompted us to compile the data obtained on anaphylactoid reactions by plasma substitutes in Table XXII. It can easily be detected that only Haemaccel definitely causes these reactions by histamine release. All the other drugs show some probabilities and possibilities of such a mechanism, but using Popper's philosophy of science (78) there is truth only in the refutation of this hypothesis: Dextran in man and dogs, hydroxyethyl starch in dogs, oxypolygelatin in man and dogs etc. cause anaphylactoid reactions without significant histamine release.

Conclusion

The fluorometric assay (combined method) for plasma histamine concentration in man and dog and for blood histamine content in dog is a reliable and relevant test. As other clinical-chemical methods it needs examination of its reliability when the conditions of the assay are changed, such as in pathological conditions.

Its application in clinical circumstances leads to a better differentiation of histamine- and non-histamine mediated reactions than other direct or indirect assays. Evidence for histamine release influences the interpretation of mechanisms involved in clinical incidents, but for itself it is not specific enough to define causes of clinical reactions.

If histamine, however, is the predominant mediator of side-effects by drugs or operation, treatment by H_1- and H_2-receptor antagonists seems to be a specific therapy and premedication in anaesthesia and surgery with a considerable future.

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Von Recklinghausen's Disease with Involvement of the Colon: An Endoscopic View

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Neurofibromatosis, a familial disease characterized by mesodermal and ectodermal dysplasia, has multiple sites of involvement. The disease can involve the skin, the central and peripheral nervous system and bone. The intestinal tract is involved in one quarter of the cases (1). The usual site of intestinal involvement is the small intestine (1–3). Colonic involvement is rare (4). This is to report a case of neurofibromatosis with involvement of the colon and to describe its appearance at colonoscopy.

Case Report

This 39-year-old male with characteristic universal cutaneous nodules and cafe-au-lait spots was evaluated for vague abdominal pain. There was no history of gastrointestinal bleeding and there was no diarrhea. Barium enema and barium meal examination of the small bowel were negative.

At colonoscopy, multiple small submucosal nodules measuring ¼ to ½ cm in diameter were seen. (Fig. 1). The mucosa between the nodules was normal. The nodular appearance of the colon extended from the rectum to the mid-transverse colon. The ascending colon and the proximal transverse colon were normal. No evidence of ulceration, bleeding mucosa or pseudopolyp formation was seen. A mucosal biopsy at the site of the nodules showed normal overlying mucosa.

Discussion

Neurofibromatosis, though rare, has to be added to the list of diseases causing multiple polypoid defects of the colon (2–5). Familial polyposis, Gardner's syndrome, Canada-Cronkite syndrome are associated with adenomas. These are mucosal lesions which protrude into the lumen of the colon. Similarly, juvenile polyps and the lesions of Peutz-Jeghers syndrome protrude into the lumen of the colon. The pseudopolyps of ulcerative colitis are irregular in size and shape and the intervening mucosa is abnormal. Neurofibromas of the colon are encapsulated and submucosal (1). Occasionally they can be pedunculated. The mucosa between the lesions is normal. They can cause partial intestinal obstruction and bleeding (6). When plexiform involvement occurs, megacolon can be seen (8). Sarcomatous change can occur (9). The usual site of the gastrointestinal lesions in neurofibromatosis is the small intestine (1–6). The ileum is most commonly involved. Marshak et al described the radiographic appearance of intestinal neurofibromatosis as multiple submucosal filling defects (3). Occasionally, pedunculated lesions can be seen. Surgical intervention has been recommended for localized disease (1). Since

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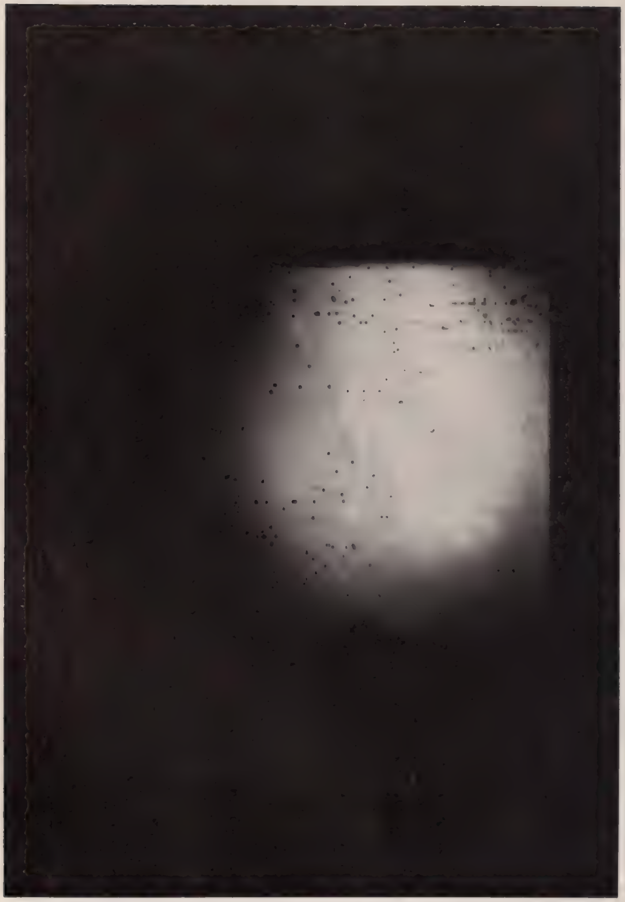

FIG. 1. Colonoscopic view of the sigmoid showing multiple small submucosal nodules.

the lesions are vascular, arteriography may be helpful in localizing the lesions associated with ulceration and bleeding.

Summary

A case of neurofibromatosis with colonic involvement has been presented. The endoscopic features include submucosa nodules with normal intervening mucosa.

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A Malignant Calvarial Doughnut Lesion ("Button Sequestrum?")

PETER M. SOM, M.D., PAUL J. ANDERSON, AND BERNARD S. WOLF, M.D.

The term "button sequestrum" was first used by Wells (1) in 1956 to describe a radiolucent calvarial defect with an island of bony density within its center. He believed that it was characteristic of eosinophilic granuloma and demonstrated four histologically proven cases which revealed destruction of the diploe and incomplete destruction of either the outer or inner table accounting for the appearance of a "sequestrum." Similar lesions had been previously reported by Tirona (7) and Meng (10) as examples of tuberculosis involving the calvarium. In their cases, greater destruction of the outer table than of the inner table resulted in the appearance of a sequestrum. Since the original description of Wells, at least twelve other entities have been described with similar Roentgen appearances. These have included metastatic disease from lung cancer and breast cancer (3, 9), staphylococcal osteomyelitis, radiation necrosis, meningioma, dermoid and epidermoid tumors, hemangiomas, fibrous dysplasia and burr holes with a tube within the hole. Satin (12) added multiple myeloma and Paget's disease to this list of differential diagnoses.

In 1969, Keats and Holt (4) described 21 cases of "doughnut lesions" as a previously undescribed entity which they believed to be inconsequential, asymptomatic, and benign. In two cases, there was histologic confirmation of the benign nature of the process which seemed to resemble a healing infarction in membranous bone. Radiographically, bony densities of varying sizes were present within central areas of radiolucency. In contrast to the cases originally described by Wells as "button sequestra," the lesions described by Keats and Holt showed a distinct sclerotic rim surrounding the lucent region. Presumably, this was the differential point between a "doughnut lesion" and a "button sequestrum" although some of the later lesions described as button sequestra showed a thin somewhat indistinct sclerotic rim around the lucent defect. Bartlett and Kishore (11) recently reported multiple benign "doughnut lesions" in a single family. In this report, tangential views were included which demonstrated distinct external elevation of the sclerotic margins. There is currently therefore, in the literature some confusion in the designations "button sequestrum" and "doughnut lesions" as well as in their pathologic nature and prognosis. The following case emphasizes the fact that a sclerotic rim demonstrated both radiographically and, on computerized tomography, may be associated with a malignant process.

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Case Report

The patient was an 83-year-old white female admitted for investigation of an organic mental syndrome. Ten years before admission, she had had a subarachnoid hemorrhage due to a ruptured aneurysm of the left posterior communicating artery. She made an excellent recovery from this episode with hypotensive medical treatment. Two years before admission, she underwent a mastectomy for carcinoma of the breast. She also suffered from chronic obstructive pulmonary disease and mild congestive failure. Multiple investigations in the hospital including isotope scans of the skeleton and the liver were negative. Conventional radiographic skeletal survey was also normal except for a doughnut type of lesion in the calvarium (Fig. 1). The patient did poorly in the hospital, developed a pneumonitis, as well as more severe congestive heart failure, and expired.

At autopsy, the calvarium showed a circular zone of relative softness in the parietal bone. This measured approximately 2 cm in diameter and was most apparent on transillumination of the bone. After decalcification and histologic sectioning, microscopic examination disclosed islands of metastatic carcinoma within fatty tissue in spaces between bony trabeculae. There was a mild to moderate osteoblastic reaction along the trabecular margins. Around the periphery of the central zone of this disc-shaped lesion, there were tumor-containing spaces without bone formation. In the center of the lesion, there were residual thin discontinuous fragments of bone in both the inner and outer tables. At the margin of the involved area, the bony trabeculae were considerably thicker and essentially represented thick cortical bone. Outside this margin, the inner and outer table and intervening cancellous bone appeared normal. No other metastases were encountered in the general autopsy examination. The site of the previous mastectomy was free of tumor. The cause of death was cardiopulmonary failure.

Discussion

Despite the original description of Wells, that a button "sequestrum" shows only a central calcific density within a radiolucent defect without a peripheral

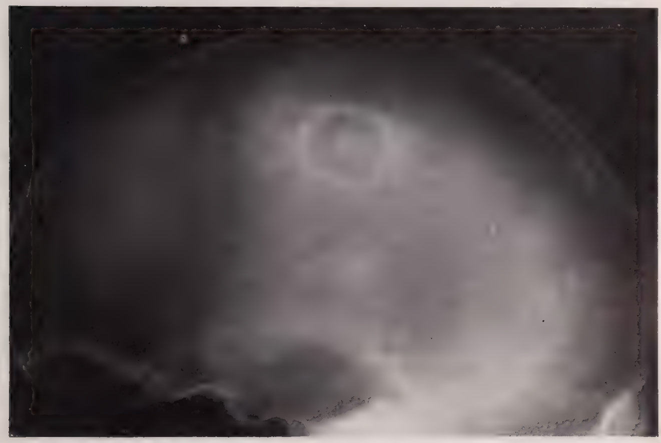

FIG. 1. Lateral skull film reveals a "button sequestrum" of the parietal bone measuring 2½ cm in diameter. There is a definite zone of increased density 3 to 4 mm wide outlining the margin of the lesion. A clearly defined bone density is located in the center.

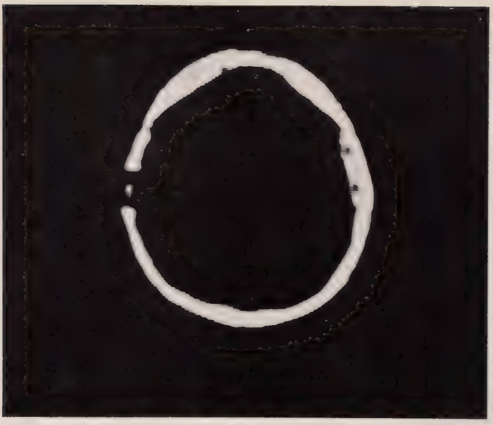

FIG. 2. Axial CT scan through the level of the lesion demonstrates the isolated bone density in the center of the lesion with increased cortical bone at the margins of the defect.

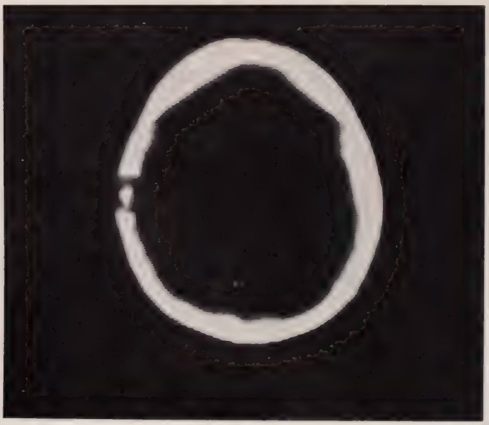

FIG. 3. Axial CT scan at the same level as Fig. 2 with a wider window setting reveals soft tissue filling the space between the calcified sequestrum and the dense margins of the lesion.

sclerotic margin, subsequent cases so designated have often included a minimal sclerotic periphery. These cases would then correspond to benign "doughnut lesions" described as such later by Keats and Holt. As this case indicates, a lesion corresponding to the description of Keats and Holt may be malignant.

It therefore appears that, in any specific case, differential diagnosis cannot be made with certainty solely on the basis of the radiologic findings. Under equivocal circumstances, a final diagnosis may require biopsy of the lesion or serial follow-up examinations.

Acknowledgment

We are grateful to Dr. Paul Slosberg for his referral of this case.

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Postoperative Nutritional Failure and Chronic Cerebral Edema in Neurosurgical Patients

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Nutritional disturbances are not usually considered of much importance in the postoperative care of the neurosurgical patient. Because most significant changes occur within the first week after craniotomy, it has even been suggested that no concerted effort is needed to correct the imbalances of fluid, electrolytes, and nitrogen metabolism (1, 2). Nevertheless, many patients with intracranial lesions are in a state of poor nutrition on admission because of an inadequate dietary intake prior to hospitalization (3). The catabolic status generally presents as a simple weight loss rather than clinically evident cachexia, and initial routine laboratory tests may reveal only mild hyponatremia and hypoalbuminemia. The institution of fluid restriction, osmotic diuretics, and steroids further alters the water, mineral, and protein balance. Subsequent to excision of a tumor from the intracranial cavity, mechanical decompression provides favorable circumstances for resolution of cerebral edema. However, some patients do not make the desired progress long after the expected period of brain swelling from operative trauma.

Shoemaker et al (4) reported the rapid onset of postoperative dishydration, or water maldistribution, in seventeen of the 602 cases admitted in 1971 to The Mount Sinai Hospital Surgical Intensive Care Unit. Two neurosurgical patients in this study and eight more over the next two years went into a neurasthenic decline during a prolonged recovery period following craniotomy. Consistent with the accepted therapy for cerebral edema, they were primarily treated with steroids, osmotic diuretics, and fluid restriction. Body compartment measurements demonstrated a depletional state with an expanded extracellular space and an intracellular deficit proportionally greater than weight loss. Hyponatremia, hypoalbuminemia, low blood volume, and intestinal malabsorption were also observed. Six of these ten patients died; treatment in the remaining four was then entirely directed toward reversal of the previously unsuspected nutritional failure.

Materials and Methods

The patients who were studied entered the hospital with symptoms and signs of an intracranial mass; the diagnosis was confirmed by cerebral angiog-

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raphy. Preoperatively, all were in fair condition; postoperatively, they recovered more slowly than expected, becoming weak, unable to eat, and responding only to painful stimuli. There was considerable weight loss, but they did not look wasted. In each case, funduscopic examination was negative, lumbar puncture revealed normal cerebrospinal fluid pressure, and no clinical signs of increased intracranial pressure were observed. None of the patients was suffering an airway problem, and blood gases were persistently within normal limits. Repeat angiography showed the cerebral vasculature to be intact, excluded hematoma formation, and demonstrated mild hemispheric swelling.

The patients were at first unable to take more than an 800-calorie tube feeding without developing diarrhea and going into negative water balance. It was elected, therefore, to feed the patients intravenously with a standard hyperalimentation regimen; protein hydrolysate and dextrose solutions with conventional additives were administered through centrally placed silicone rubber catheters. Blood volume deficits and hypoalbuminemia were initially treated with blood transfusions and 5% albumin. Throughout this period of intravenous alimentation, tube and later oral feedings were continued and increased as gastrointestinal function improved. Intravenous feeding was employed until the patient could manage an oral diet over 2,000 calories; within this same interval, tube feeding was also discontinued.

Daily intake and output of water, sodium, and potassium were measured until the patient's diet was too varied to make accurate determination possible. Weights were taken every day before breakfast. Full routine biochemical and hematologic testing was performed twice a week.

Plasma volume was measured by the indicator dilution technique with I^{125} labeled human serum albumin. Blood volume was calculated as the plasma volume divided by one minus the corrected hematocrit expressed as a percent. The volume of dilution of Br^{82} was used as an estimate of the extracellular fluid, and dilution of heavy water as a measure of total body water. The intracellular fluid was computed as the difference between total body and extracellular water.

Results

Case 1. A 59-year-old man (Fig. 1) underwent occipital craniectomy for removal of a recurrent hemangioblastoma of the cerebellum. For the first three postoperative days, a ventilator was required due to central apnea. When tube feedings were instituted, his attendants were rewarded with diarrhea. Five weeks later, his weight had dropped from 85 to 65 Kg; and as he was in true coma and appeared to be dying, discharge from the intensive care unit was contemplated. Although he lost less than one quarter of his normal body weight, his intracellular space had halved. His extracellular space had expanded to give him a normal body water for his current weight. His serum albumin was 2.5 Gm%, serum sodium 129 mEq/L, hematocrit 27%, and blood volume 72% of expected. The response to a 4,000 calorie intravenous hyperalimentation diet was dramatic. Over five days, he absorbed 700 mEq of potassium. By the

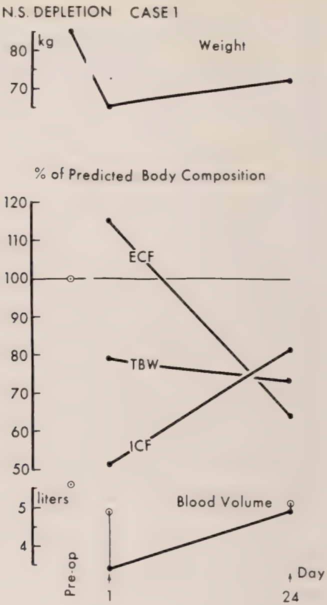

FIG. 1. Note progressive increase in ICF and decrease in ECF in relation to TBW. Predicted norms for blood volume are represented by small circles and deficits by vertical lines.

sixteenth day, he could drink from a cup and took cognizance of his surroundings by demonstrating open hostility toward his mother. By the twenty-fourth day, he could make pleasant conversation, even telling humorous anecdotes. There was an acceptable increase in intracellular fluid, and he was able to ambulate with only mild ataxia.

Case. 2. A 39-year-old woman (Fig. 2) underwent frontal craniotomy for clipping of a left anterior communicating aneurysm. Over the first three postoperative days, she developed drowsiness, right hemiplegia, and aphasia. Angiography documented left middle cerebral artery spasm. Three weeks later, she was unarousable and had lost 11 Kg. Repeat angiography revealed only hemispheric swelling. Her serum albumin was 2.8 Gm%, and serum sodium 128 mEq/L. She was placed on a 3,000 calorie parenteral diet, and for five days had a positive potassium balance of 550 mEq. She then awoke suddenly, kissed her husband, and cried when shown photographs of her children. She continued to take considerable nutrition by mouth, regained use of her right side, and was discharged home.

Case 3. A 60-year-old woman (Fig. 3) underwent left craniotomy for removal of a tentorial meningioma. Her wound failed to heal, and she was treated with antibiotics for two episodes of meningitis. During the first two postoperative

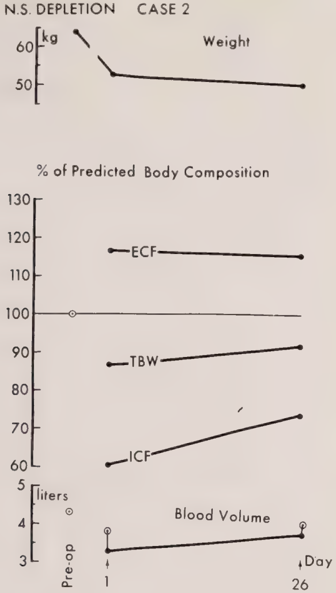

FIG. 2. Note 2.2 liter increase in ICF despite 3 kilogram weight loss.

weeks, mechanical support of her respiration was necessary. After a full month of standard intravenous fluid replacement, there was a 70% deficit in expected intracellular space. Her serum albumin had risen from 1.3 to 1.6 Gm%. A 4,000 calorie parenteral diet was begun and continued until an oral intake of 2,000 calories was possible without diarrhea. She had an intermittently positive potassium balance averaging 20 mEq per day. After two weeks of hyperalimentation, her incision could be reclosed surgically. By the third week, she was sitting out of bed, became very talkative, and fed herself. At the end of ten weeks of nutritional therapy, her space measurements were in normal range; and she could walk with minimal assistance. Her memory improved, and she regained her sense of humor.

Case 4. A 56-year-old woman (Fig. 4) underwent left frontotemporal craniotomy for excision of a convexity meningioma with hyperostosis followed two weeks later by a right frontal craniotomy for removal of a parasellar meningioma. She had a residual left hemiplegia and remained febrile and somnolent for five weeks. Her weight had fallen from 70 to 60 Kg, and her intracellular space was 66% of expected. Her serum sodium was 128 mEq/L. A 3,000 calorie parenteral diet was instituted. During the first ten days, she had a positive potassium balance of 300 mEq. She was then able to sit up in a chair and

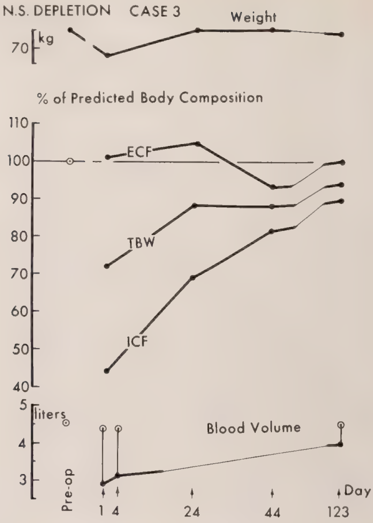

FIG. 3. Note two-fold increase in ICF without remarkable weight change.

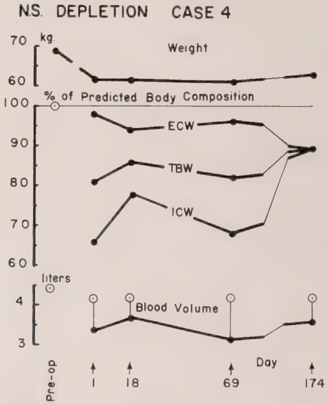

FIG. 4. Note one-third increase in ICF without remarkable weight change.

absorb tube feedings. Two weeks of antibiotic therapy were required for an infected subclavian catheter site. After one month of hyperalimentation, her intracellular fluid returned to 88% of expected. She was alert and able to eat by herself. At ten weeks, active physical therapy was begun. Her left hemiplegia resolved over a three-month period, and a left cranioplasty was performed. She was discharged from the hospital and resumed her preoperative plans of separating from her husband.

Discussion

Electron microscopy has shown that edema in gray matter is characterized by swelling of the cellular elements (5). The hydrops is more evident in the perivascular feet of astrocytes and dendrites than in the oligodendroglia. Alterations of virtually all cytoplasmic organelles occur, but the mitochondria are the earliest to be affected. In marked contradistinction, the edema fluid in white matter is extracellular with evolving expansion of the Virchow-Robin spaces. Separation and vacuolization of the myelin sheath, as well as formation of lacunae in the cytoplasm of oligodendrocytes, are regularly observed. The regions of the brain that normally have a high water content—arcuate zone, corpus callosum, and internal capsule—exhibit minimal disruption (6).

Biochemical analysis of edematous tissue adjacent to human brain tumors has contributed further to an understanding of the basic pathology (7). Determinations of water content confirm that the increase in volume of the white matter (25%) is about three times that of the cortex (8.6%). The edema fluid accumulated within the cerebral cortex has an amazingly high sodium concentration of 280 mEq/L, whereas the concentration in swollen white matter is about 125 mEq/L. The loss of potassium from the affected gray matter is about one-third of the sodium increase. Studies of the energy stores in human edematous cortex reveal that the concentrations of creatine phosphate and adenosine triphosphate are low, while adenosine diphosphate and monophosphate and inorganic phosphate are above normal. The lowered level of glucose and corresponding rise of lactate are additional evidence of anaerobic glycolysis and tissue hypoxia consistent with mitochondrial dysfunction. The build up of free fatty acids from the breakdown of lipids further impairs oxidative phosphorylation and neuronal function (8).

The effect of glucocorticoids on cerebral edema is not well defined, but diminished brain size has been demonstrated angiographically (9); reduced swelling of astrocytes and lessened accumulation of extracellular fluid in white matter have been documented with the electron microscope (10). Rapid intravenous administration of hypertonic urea or mannitol solutions reduces cerebrospinal fluid pressure for three to five hours. A secondary rise in pressure, which can be prevented by dehydration, occurs when one third of the urine output is replaced intravenously; in the event of an intracranial mass, fluid restriction was found to be totally ineffective (11). There is little electron microscopic change in the picture of cerebral edema after osmotic diuresis (12). The rapid shrinkage of the entire cerebrum observed macroscopically probably results from dehydration of intact brain tissue, but withdrawal of fluid and electrolytes from edematous areas may occur later (13).

Conclusion

The pathophysiology of chronic cerebral edema involves a generalized metabolic derangement. Conventional therapy is not directed toward the continuous supply of metabolically produced energy required for the support of normal glial and neuronal structure and activity. Early postoperative treatment of protein, water, and mineral imbalances provides favorable circumstances for return of neural function in the chronically edematous brain. The syndrome has virtually been eliminated in neurosurgical patients at Mount Sinai Hospital over the past three years.

Our data suggest 1) that after the predictable period of surgical swelling, treatment with steroids, osmotic diuretics, and fluid restriction should be abandoned; 2) that following angiographic documentation of unremitting cerebral edema, a full high caloric diet should be instituted for intensive nutritional therapy; and 3) that although the vast majority of neurosurgical patients make an appropriate recovery without specific attention to nutrition, correction of shifts in the body fluid compartments appears to be essential for postoperative resolution of chronic cerebral edema.

Summary

Ten patients, following uncomplicated craniotomy for removal of an intracranial mass, became increasingly comatose over a two to five week period even though conventional therapy for cerebral edema was in progress. postoperative angiography showed only mild hemispheric swelling. Despite unremarkable serum chemistries on admission, body composition studies revealed unsuspected nutritional failure. There were no airway problems and no clinical signs of increased intracranial pressure. Six of the patients died; high doses of steroids, osmotic diuretics, and fluid restriction were discontinued in the remaining four. Subsequent therapy was entirely directed toward hyperalimentation, progressing from intravenous to tube feeding to oral regimens. With return of the space measurements to normal, appropriate neurological recoveries were observed. Electron microscopy and laboratory studies of the edematous brain are discussed. The rationale for postoperative treatment of chronic cerebral edema and generalized neural dysfunction by nutritional therapy is presented.

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Focal Arteritis of Uterus: A Case Report

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Abstract

A case of focal arteritis of the uterus, histologically compatible with periarteritis nodosa, is reported. The patient has been observed for four years without any therapy for this lesion and systemic symptoms have not appeared. The benign nature of focal arteritis in the uterus is discussed.

Introduction

We have observed a patient with focal arteritis histologically compatible with periarteritis nodosa in the uterus for four years. No therapy was administered, and since no other symptoms have occurred during this time, we are reporting this case as evidence for the benign nature of focal arteritis or focal periarteritis nodosa as distinct from the generalized form.

Case Report

A 34-year-old black female, para 3 and gravida 3, was admitted to City Hospital Center at Elmhurst on August 26, 1973, because of "pressure" in the vagina and stress incontinence. Her last delivery was in 1965; and until the previous few months, she had been on contraceptive pills. Since then she had inserted jelly intravaginally for contraceptive purposes. She had pulmonary tuberculosis in 1956 and was treated with streptomycin and para-aminosalicylic acid. She suffered a traumatic pelvic fracture in 1958 and blood was administered at that time. She denied allergy, hypertension and arthritis. Occasionally, she felt pain in the right shoulder for which she was given Robaxin and Tylenol. She was regularly followed in the medical clinic. One month prior to admission, she had a common cold.

On admission, her blood pressure was 120/80 mmHg and body temperature 98.6°F. The eyes, nose and mouth were unremarkable. There was no cervical lymphadenopathy or thyroid enlargement. The heart and lungs were normal. No masses were palpable in the breasts. The liver and spleen were not palpable. The skin was unremarkable. The pelvic examination revealed a moderate degree of cystocele and rectocele. The hemoglobin was 11.6 gm.%, hematocrit 33%, white blood cell count 7,300 cu.mm. with normal differential count. Erythrocyte sedimentation rate was 55mm in the first hour (Westergren). Hepatitis-associated antigen was not present and VDRL was negative. The urinalysis showed no albuminuria or hematuria. The blood chemistries were within normal limits. The chest x-ray showed no active tuberculosis or scars. Nonspecific T wave change was seen in the electrocardiogram. Vaginal hysterectomy was performed and she recovered uneventfully and was discharged on the 15th hospital day. The patient has been followed for 4 years and is in good health.

Pathologic Examination

The uterus measured 9.5 × 5.0 × 3.5 cm and weighed 100 gm. It was of normal shape. The serosal surface was smooth and glistening. The myometrium and cervix were unremarkable. The endometrium showed fresh post-curetting hemorrhage.

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Microscopically, many scattered groups of small to medium-sized arteries in the uterine body and cervix showed necrosis of the arterial walls with polymorphonuclear cell and lymphocytic infiltration within the wall and perivascular spaces (Fig. 1 and 2). The internal elastic lamina was disrupted or completely destroyed and aneurysmal dilatation was occasionally seen (Fig. 3). Fibrin

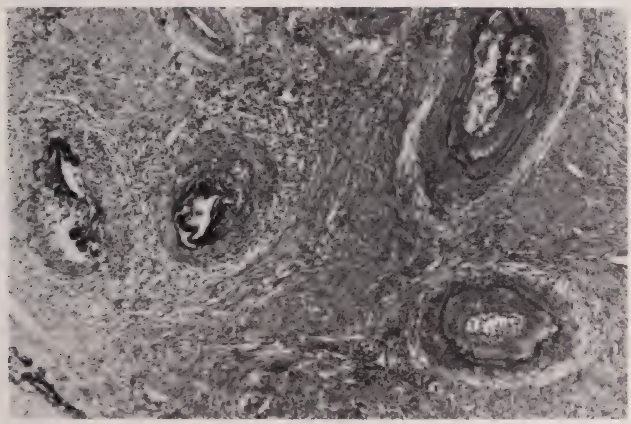

FIG. 1. A group of arteries in the myometrium showing necrotizing arteritis (Elastic Van Gieson Stain 60×).

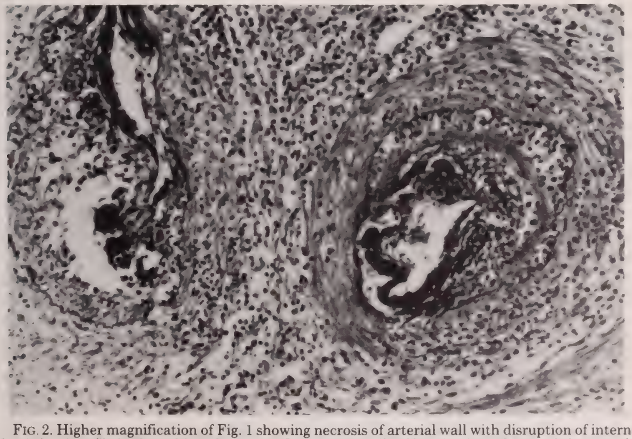

FIG. 2. Higher magnification of Fig. 1 showing necrosis of arterial wall with disruption of internal elastic lamina, fibrin thrombi, and severe inflammatory cell infiltration in and around the vascular wall (Elastic Van Gieson Stain 145×).

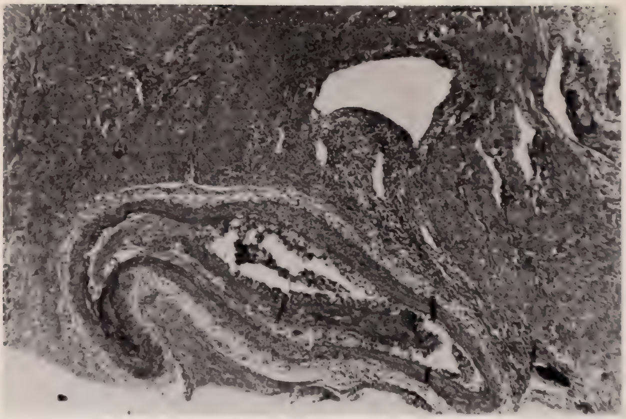

FIG. 3. Segmental necrotizing inflammation of an artery with aneurysmal dilatation and thrombosis (Elastic Van Gieson Stain 50×).

thrombi were frequently present. The major arteries at the site of penetration into the uterus were not involved. No giant cells were seen in the vascular lesions. The vascular changes were characteristic of periarteritis nodosa and unlike giant cell arteritis (1, 2).

Discussion

Although periarteritis nodosa usually presents as a systemic disease, focal vascular lesions resembling those seen in periarteritis nodosa have been seen limited to one organ such as the appendix (3), gallbladder (4), and skin (5). Plaut (3) reported 88 cases of focal arteritis in surgically removed appendices and 1 in a prolapsed uterus in 1951. He stressed the benign clinical course of patients with the focal lesion as compared with the severe prognosis in generalized periarteritis nodosa, although morphologic changes in the vessels in both the focal and generalized disease were identical.

Recently, Ansett et al (6) have observed 10 cases of focal arteritis of the uterine cervix without involvement of the corpus. These cases have been followed from several months to 15 years without manifestations of systemic disease. Since the progression of focal arteritis to systemic periarteritis nodosa has never been reported, the focal type may be a benign form of this disease or a totally different entity. It is important to be aware that the findings of arteritis or periarteritis nodosa in a removed uterus does not necessarily signify a generalized vascular disease but that the vascular lesion may remain localized to the uterus without involvement of any other organs.

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Basal Cell Carcinoma of the Vulva

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Introduction

Basal cell carcinoma, an infrequent vulvar neoplasm, accounts for approximately 2–4% of all primary malignant tumors of the vulva (1–3). This tumor has an inconstant gross appearance (1, 2, 4–6), and is associated with a protracted symptomatic interval prior to diagnosis (1, 2, 7), a tendency towards recurrence (2, 7), and very rare metastases (8).

The cases of four patients with five basal cell carcinomas of the vulva, representing the sum of cases diagnosed at this hospital over a 23-year period (1953–1975) are presented, to alert the clinician to the existence of this lesion and to its natural history (Table I).

Case Studies

Case One: L. B., a 73-year-old Caucasian female, presented to her physician with a painless 4 mm., slightly raised, nodule with indurated white margins, that had been present on the midportion of the left labium majus for 15 months. Wide excision for a possible "carcinoma" was performed; the histologic diagnosis of basal cell carcinoma was made.

Fifteen years later, a second nodule appeared on the right labium majus, just inferior to the mons pubis, and to the right of the clitoral hood, and gradually increased in size. The diagnosis of basal cell carcinoma was made, which was confirmed histologically after excision.

During this fifteen year interval, a cutaneous squamous cell carcinoma was removed from the chest, and basal cell carcinomas were excised from the gluteal cleft, right eye region, and right side of nose. The patient died of a myocardial infarction two years later at the age of 90, without vulvar recurrence.

Case Two: I. L., a 71-year-old female, developed a painless, slowly growing cystic lesion of the left labium. There was a single episode of lesional bleeding. The tumor was excised one year subsequently, with the diagnosis of vulvar cyst. It measured 1 cm in diameter, and contained yellowish clear fluid. A cystic basal cell carcinoma was seen on microscopic examination (Fig. 2).

The patient was well, and without recurrence, nine years after surgery.

Case Three: D. H., a 67-year-old Caucasian female, sought medical advice with a three-year history of occasional vulvar pruritis with bleeding after scratching. Physical examination disclosed a 3 to 4 mm superficial ulcer with an erythematous border, that was located at the inferior margin of the right

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TABLE I

Basal Cell Carcinoma of Vulva

Case #	Location	Symptoms	Appearance	Treatment	Outcome
1	Left labium majus	Painless nodule present 15 mos	4 mm raised, indurated nodule	Wide excision	No recurrence
	Right labium majus	Nodule		Excision	No recurrence, pt. died from MI 17 years after, first, 2 years subsequent to the second vulvar excision
2	Left labium	Painless cystic lesion present 12 months	1 cm cyst	Excision	No recurrence 9 years after excision
3	Right labium majus	Vulvar pruritis 3 years	4 mm superficial ulcer	Wide excision	No recurrence 8 years after excision
4	Right labium majus	Nodule present 3 years; Frequently drained;	Pigmented soft lesion	Excision	Recurrence 6 mos. later
		Recurrence in scar		Wide Excision	No recurrence 4½ years after second excision

labium majus with the perineum. A diagnosis of tumor was made, and a wide local excision removed a superficial basal cell carcinoma.

The patient was free from recurrence eight years after excision.

Case Four: V. G., a 56-year-old, Caucasian female had a three-year-history of a mass of the superior right labium majus. The lesion was thought to be an infected subaceous cyst, because it was repeatedly drained. After becoming "infected" a local excision removed a pigmented solid basal cell carcinoma (Fig. 2).

Six months later, a 3 × 3 mm recurrence in the surgical scar was widely excised. The patient had a basal cell carcinoma removed from the skin of the right temple two years later.

The patient was alive and without recurrence five years after the original vulvar excision.

Discussion

The clinical and pathologic features of basal cell carcinoma of the vulvar skin in the main parallel those of non-vulvar, cutaneous, basal cell carcinoma. It is a disease of the late post-menopausal age group. Mean ages of 58–73 years have been reported (1, 4, 5, 7) although occasional cases have been discovered in women in the fourth and fifth decades (1, 2). Cases occurring in black women are rare (1, 7).

Symptoms usually consist of an awareness of a painless nodule or pruritis (1, 2, 4). Excoriation frequently produces lesional bleeding. The duration of

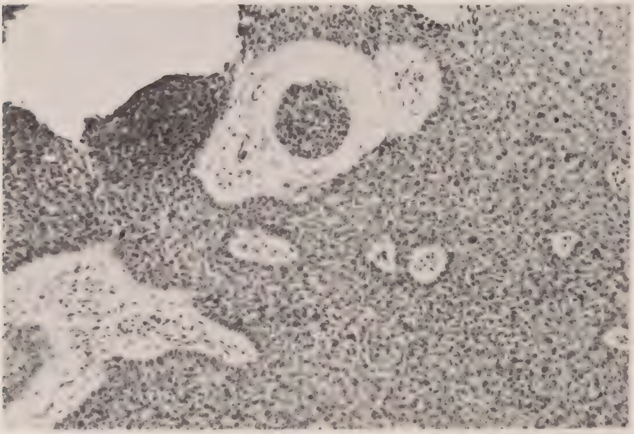

FIG. 1. Case 2. Primordial basal cell carcinoma. Solid nests of basal cells, with peripheral palisaded nuclei, and edge of cystic cavity (H & E × 50).

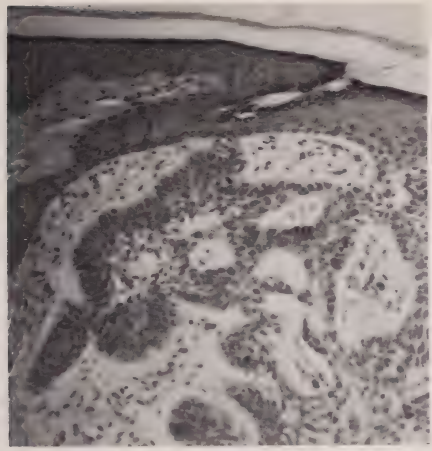

FIG. 2. Case 4. Primordial basal cell carcinoma with abundant fibrous stroma. Tumor nests are confluent with squamous epithelium of surface and of shaft of hair follicle (H & E × 128).

symptoms is usually protracted, with the delay prior to seeking medical advice often reaching several years (1, 2, 7).

The great majority of lesions are located on the labia majora (1, 2, 4). The mucosa of the labium minora and the clitoris has been the primary site in only about 10% of recently recorded cases.

The appearance of the tumor is extremely variable—a nodule or an ulcer are the most frequent clinical appearances, but papillomas, erythematous plaques, leukoplakia and cysts have been described (1, 2, 4–7). Pigmentation is occasionally seen, and has led to the misdiagnosis of "nevus." The size of these lesions is also variable, and ranges from several mm. up to 3 cm, although the usual size is about 1 cm in diameter (1, 2).

The diagnosis is rarely made prior to excision, possibly because of the varied clinical presentation and the lesion's rarity.

In Palladino's extensive review of the literature, about 20% of patients have developed another cutaneous or visceral carcinoma (2). Not surprisingly, basal cell carcinomas arising in non-vulvar skin have been the most frequently associated neoplasm. Rarely, a second basal cell carcinoma may occur on vulvar skin (Case One). Single cases of vulvar squamous cell carcinoma and malignant melanoma have been reported (2) in association with vulvar basal cell carcinoma, and undoubtedly represent merely a fortuitous circumstance.

No association has been established with preexistent vulvar dystrophy, arsenical therapy, or vulvar inflammatory disease, granulomatous, venereal, or otherwise (1, 2). At least three patients had received vulvar irradiation, between ten and thirty years prior to diagnosis of the vulvar carcinoma (1, 2). No etiologic agent could be postulated for any of the four present cases.

The histologic types of basal cell carcinoma parallel that of cutaneous basal cell carcinoma in general (4).

Local excision that widely and completely removes the tumor should be adequate therapy (1, 4, 7). The recurrence rate for this lesion approximates 20% (2, 7). Only one reported instance of metastasis, that to inguinal nodes, has been reported (8).

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Eisenmenger Syndrome—Anesthetic Management for Labour and Delivery: A Case Report

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Eisenmenger syndrome includes a multiplicity of congenital heart conditions characterized by pulmonary hypertension due to high pulmonary vascular resistance with reversed or bidirectional shunt at the aortopulmonary, ventricular or atrial levels. The clinical picture is that of a progressive increase in exertional dyspnea and cyanosis. Repeated hemoptysis and sudden death is common (1).

Pregnancy and delivery in these patients are associated with a high maternal mortality rate. Jones and Howitt reported a mortality rate of 27 percent (10 out of 37 pregnancies) (2), while Neilson et al reported 4 deaths in 9 pregnancies (3).

Case Report

This patient (28-year-old) was first diagnosed as suffering from congenital heart disease at the age of 4. Cardiac catheterization then confirmed the presence of a ventricular septal defect, severe pulmonary hypertension 110/55 torr, a left ventricular pressure of 110/8 torr and bidirectional shunt (oxygen saturation in right atrium being 66.5%, in right ventricle being 83.5% and in left ventricle 93.0%). Subsequent catheterizations at age of 12 and 18 revealed similar values. She had had one spontaneous abortion at the age of 26, following an attack of pneumonia.

She was first seen at the Mount Sinai Medical Center Prenatal Clinic, when a pregnancy of 12 weeks was diagnosed. Clinical examination revealed that she was not cyanotic, with normal venous pressure, no finger clubbing. She experienced dyspnea on moderate exertion (New York Heart Association—function Class II) (4). The right ventricle was hypertrophied and a loud pulmonary second sound was heard. Electrocardiogram showed severe right ventricular hypertrophy, right axis deviation and first degree heart block. Chest x-ray showed prominent right ventricle and main pulmonary arteries, with peripheral oligemia. Hemoglobin was 16.4 gm%. Arterial blood gas analysis revealed a pH of 7.43, PCO_2 37.8 torr, PO_2 60 torr, and base excess of −4.6 mEq/L (FiO_2 0.2).

Termination of pregnancy was advised, but the patient adamantly refused. She was then observed regularly in the prenatal clinic and admitted into hospital at 18 weeks of pregnancy for observation and rest. Weekly laboratory investigations showed a haemoglobin level averaging 14.6 gm%, Hct 47.2% and arterial blood gases, on room air, in the following range pH 7.39 to 7.43, PCO_2 32 to 28/torr PO_2 59 to 70 torr and base excess-4.0 to-5.0 mEq/L. Frequent sonograms indicated normal fetal development. Heparin therapy was started from the 22nd week (5,000 μ given intravenously every six hours), and this was discontinued two days before delivery. From the 24th week the patient developed progressive decrease in functional capacity, dyspnea occurring after mild exertion (NYHS class III) (4).

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Labor and Delivery

At 36 weeks of pregnancy, spontaneous labor began at 4 a.m. She was transferred to the Coronary Intensive Care Unit. At 5:45 a.m. an epidural catheter was introduced through the 3rd–4th lumbar intervertebral space followed by a dose of 4 ml. of 2% Nesacaine. A Swan-Ganz catheter, a radial arterial line and a peripheral venous line were established. Systemic and pulmonary arterial pressure, blood gases, (TAB.1) as well as maternal and foetal electrocardiogram were monitored continuously. Morphine sulphate 5 mg was given intravenously at 7:35 a.m. to supplement the analgesic effect of epidural anesthesia and to avoid the emotional reaction, which could cause tachycardia and further hemodynamic changes. 100% oxygen was administered through a face mask.

Because of slow progress of labour, a Pitocin infusion was started at 8 a.m. At 8:35 a.m. the cervix was 5 to 6 cm dilated. Nesacaine 2 percent solution was given in increments of 4 ml, at intervals of about 30 minutes, in combination with intravenous morphine sulphate to achieve pain relief and at the same time maintaining steady blood pressures. The second dose of morphine sulphate, 5 mg, was given at 9:35 a.m. At 10:31 a.m., after episiotomy, a 2330 gm female infant was delivered by low forceps. The placenta was delivered and Pitocin 10 units was given intravenously.

Because of a sudden drop in systemic blood pressure (table 1) after delivery (100/60 torr), a unit of whole blood was administered through a Pall microfilter. Estimated blood loss was 500 ml. The patient was comfortable throughout delivery.

The infant was depressed and apneic after delivery. Apgar score at 1 minute being 4 (zero for respiration and one for heart rate, muscle tone, colour and reflex irritability). Neonatal narcan (nalloxone) 0.02 mg was given intravenously and oxygen via a face mask. She responded promptly and the Apgar score at 5 minutes was 9 (minus one for colour). The infant was admitted to the Premature Nursery and thrived well.

Maternal Postpartum Course

The patient's condition remained satisfactory, her blood pressure and blood gas readings were stable. (table 1) Six hours after delivery, heparin therapy (5,000 u intravenously every 6 hours) was started, but was discontinued after 3 doses as a large haematoma developed around the episiotomy wound. The Swan-Ganz catheter was removed on the first day postpartum. Parenteral antibiotics were continued. The perineal hematoma gradually resolved over the next few days.

Discussion

The two major hazards facing a pregnant woman with Eisenmenger Syndrome are, firstly, a sudden change in the direction or ratio of the intracardiac shunt, and secondly, thromboembolism. The first condition can result from either a fall in systemic blood pressure or a rise in pulmonary vascular resistance (2).

The greatest risk occurs during delivery and in the immediate post-partum period. It is generally agreed that caesarean section should be avoided if possible. Blood loss is unpredictable. Either general anesthesia, with intermittent positive pressure ventilation, or regional block with extensive sensory and autonomic block carries high risks (5).

Vaginal delivery is considered the method of choice (2). Epidural block provides the best form of analgesia provided that maternal hypotension is avoided (5, 6, 7). The patient can be spared a painful and exhausting labor, preventing or reducing maternal distress and metabolic acidosis.

Hypotension is always a possible complication of epidural block. This can be minimized by employing the selective block technique (6), and restricting the dose of local anesthetic agent to the minimum that can achieve pain relief. In

TABLE I

Time	Heart Rate (per min.)	Blood Arterial Pressures		PO2		O2 Saturation		Arterial pH
		Systemic (torr)	Pulmonary (torr)	Systemic (torr)	Pulmonary (torr)	Systemic %	Pulmonary %	
7:00 a.m.	84	132/59	108/37	79.7	50.7	94.5	85.4	7.41
8:25 a.m.	88	130/60	106/45	87.5	52.0	96	86.5	7.43
8:40 a.m.	116	151/66	127/38	69.5	46.7	92.8	82.1	7.41
10:05 a.m.	96	140/60	116/50	95.1	85.3	96.5	94.9	7.41
10:31 a.m. Delivery	110	100/60	105/50	72.4	65.3	93.1	90.2	7.41
10:35 a.m.	96	125/65	115/45	109.9	92.2	97.3	95.9	7.38
11:50 a.m.	79	123/56	103/65	73	68.6	93.3	91.9	7.41

our case, we used a combination of epidural block and intravenous morphine sulphate to provide this relief with least disturbance of systemic blood pressure. The fetal depression caused by the narcotic can be readily reversed with narcan. Should hypotension occur, a peripheral vasoconstricting agent such as neosynephrine, is appropriate, reducing the risk of myocardial stimulation (2). Proper positioning with the patient on her side and legs elevated also helps to improve venous return. Blood loss may also be a cause of hypotension. Blood loss should be replaced by blood transfusion, preferably using fresh blood through a microaggregate filter.

Thromboembolism is a well-known hazard of pregnancy in Eisenmenger syndrome. It can result in a sudden rise of pulmonary vascular resistance. Massive pulmonary embolism is uncommon, but small pulmonary emboli can trigger off widespread pulmonary vasoconstriction (2). Heparin was given to our patient in the second and third trimester as prophylaxis against thromboembolism. However, it was discontinued because its effectiveness is not widely accepted and the disturbed clotting mechanism would contraindicate epidural analgesia (5, 6, 7). Anti-coagulant therapy in the postpartum period may also cause bleeding problem, as happened in our patient. Early ambulation is, perhaps, as important.

Summary

The outcome both of the mother, with Eisenmenger Syndrome, and the child were excellent. Vaginal delivery, under continuous epidural anesthesia and small dose of narcotic was accomplished without distress. The hemodynamic state was not significantly disturbed. Thromboembolism did not occur.

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Guillain-Barré Syndrome in a Patient with Hodgkin's Disease*

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Abstract

A case of a Guillain Barré syndrome occurring in a patient with Hodgkin's disease in relapse is described. The CSF showed albuminocytologic dissociation. Cytocentrifuge studies showed abnormal histiocytic cells. Combination chemotherapy for Hodgkin's disease resulted in complete resolution of the syndrome. We believe this is the first report of successful treatment of Guillain Barré syndrome secondary to Hodgkin's disease.

Acute infective polyneuritis first described by Guillain, Barré and Strohl in 1916 is characterized by an ascending symmetrical flaccid paralysis (1). It is felt first in the distal portions of the limbs and ascends to involve the entire limb. The weakness progresses as a rule to complete paralysis of the limbs, and sometimes to the thoracic and abdominal muscles. Sensory disturbances are usually absent. Examination of the cerebrospinal fluid shows a markedly elevated protein in contrast to the white cells which are usually low and when present are lymphocytes. We report a patient with Hodgkin's disease who developed a Guillain-Barré syndrome which presented a difficult diagnostic problem.

Case Report

A 23-year-old white male, MSH #960282, was diagnosed as Stage III mixed cellularity Hodgkin's disease after staging laparotomy and splenectomy in 1973. The spleen was involved at laparotomy. The patient was treated with total nodal radiation by the moving strip technique. He then remained disease free until 1976 when he noted weakness of his legs beginning distally and progressing proximally and paresthesias of his fingertips and toes. When admitted to Mount Sinai Hospital he was unable to walk. Neurologic examination showed marked symmetrical muscle weakness of the lower extremities, proximal more severe than the distal. He was unable to walk or stand from a sitting position. Upper extremities also demonstrated symmetrical muscle weakness. Sensory examination was unremarkable. There were enlarged cervical, axillary and hilar nodes. Cerebrospinal fluid protein was very elevated at 560 mg%. There were 2 RBC's and 1 WBC/mm^3. On cytocentrifugation 34 lymphocytes and 33 histiocytic cells, some of which appeared abnormal were seen (Fig. 1). Brain scan and CAT scan of the skull were within normal limits. A diagnosis of possible Guillain-Barré syndrome was made. The patient was initially treated with prednisone with minimal improvement in his neurologic status. Lymph node biopsy showed mixed cellular Hodgkin's disease and a diagnosis of Hodgkin's disease with meningeal involvement was made. The patient was treated with CCNU, bleomycin, prednisone and procarbazine with an excellent response. Five weeks after treatment he was able to walk without crutches. Paresthesias were gone. CSF protein was 320 mg% and there was 1 WBC/mm^3. Cytocentrifugation showed 18 lymphocytes and 2 histiocytes. Ten weeks after the start of treatment the patient was completely

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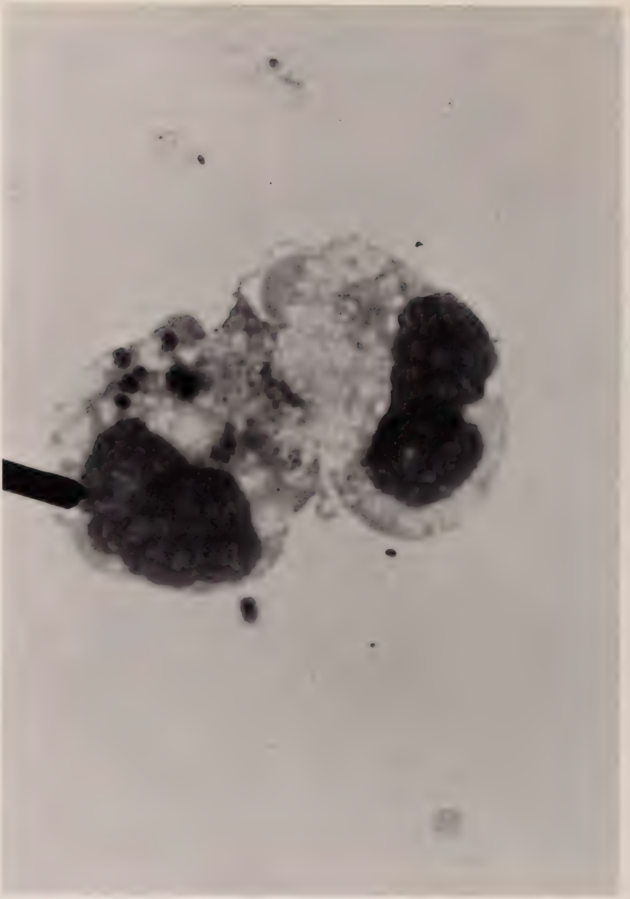

FIG. 1. Abnormal histiocytes seen on cytocentrifuged specimen of CSF.

asymptomatic. Neurologic examination was entirely within normal limits. There has been complete regression of the cervical and hilar adenopathy. A repeat lumbar puncture showed a protein of 108 mg% and 1 WBC and 9 RBC's/mm^3. Cytocentrifugation showed 23 lymphocytes, 17 normal appearing histiocytic cells and 4 segmented neutrophils.

Comment

We believe the neurologic findings were due to involvement of the meninges and probably the dorsal roots by Hodgkin's disease. The finding of abnormal histiocytic cells in the CSF and the excellent response to chemotherapy adds credence to the theory.

An alternative hypothesis is that the Guillain-Barré syndrome in our patient resulted from an immunocomplex disease or as a consequence of altered T lymphocyte function such as has been postulated as the cause of the nephrotic syndrome seen in patients with Hodgkin's disease (2, 3). Patients with nephrotic syndrome respond to therapy directed at their Hodgkin's disease. Renal biopsies do not show direct involvement by Hodgkin's disease.

The association of an ascending symmetrical flaccid paralysis and the finding of a very elevated CSF protein led to the diagnosis of Guillain-Barré syndrome in a patient with Hodgkin's disease. Treatment with prednisone was not successful. The finding of clinical relapse with cervical and hilar adenopathy and the presence of abnormal histiocytic cells on the cytocentrifuged specimen of the CSF we feel are compatible with the diagnosis of Hodgkin's disease with CNS involvement. Kaufman reported a patient who presented with a Guillain-Barré syndrome and died with progressive neurological impairment (4). At autopsy Hodgkin's disease was found with involvement of the brain, meninges, posterior roots, stomach, jejunum, gallbladder and abdominal lymph nodes. Guillain-Barré syndrome has also been reported in a patient with reticulum cell sarcoma (5). This patient also had a rapidly fatal course. Cavanagh et al reported two patients with Hodgkin's disease who developed a rapidly fatal neurological illness (6). Cerebral demyelination was found at autopsy. Cerebral demyelination associated with Hodgkin's disease has also been reported by Astrom et al (7). These patients all died with progressive neurological disease. Granulomatous angiitis of the central nervous system has been found to be associated with Hodgkin's disease. Greco and colleagues reported a patient who had a brain biopsy verifying this disorder and who responded to local radiotherapy to the neck and mediastinum with resolution of his neurologic deficity (8). We believe this is the first report of a patient with a Guillain-Barré syndrome associated with Hodgkin's disease who has responded to treatment. We feel this is due to the prompt recognition of the relationship of the neurologic syndrome to Hodgkin's disease and the equally prompt institution of combination chemotherapy including the drug CCNU which crosses the blood brain barrier.

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Chronic Thrombotic Thrombocytopenic Purpura: Report of a Case with Five Relapses and Review of the Literature

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Abstract

Thrombotic Thrombocytopenic Purpura (TTP) is a rare disease with a high mortality. Chronic TTP is a rare variant of this disorder. We report a patient with a 12-year history of TTP in whom there have been 4 relapses. Serial hematologic studies have confirmed the Coombs negative hemolytic anemia, thrombocytopenia and red cell fragmentation. Coagulation studies have not shown any consistent abnormality. A review of the literature shows 8 other reported cases 5 of whom have died at the time of relapse. The present patient and the surviving patient from the literature who had relapses rather than continuously active disease have been treated at the time of relapse with an agent that interferes with the aggregation of platelets.

Introduction

Thrombotic thrombocytopenic purpura (TTP) was first described by Moschowitz in 1925 and is characterized by a pentad of findings: hemolytic anemia, thrombocytopenia, fever, fluctuating neurological findings and renal disease. (1) Since the initial report in 1925 over 300 cases have been reported. Chronic thrombotic thrombocytopenic purpura is a rare variant of this disorder. We have followed a patient for over 12 years with TTP who has had five relapses. We have been able to find only eight other reported cases in the English literature.

Case Report

First admission. The patient was a 35-year-old white female when first seen in November 1964. She had a sore throat and had been given penicillin. One week later she noted dark urine. At that time she was hospitalized and found to have an anemia and thrombocytopenia. She developed a transient hemiparesis and was transferred to Mount Sinai Hospital. The patient was febrile on admission and had numerous ecchymoses. The hemoglobin was 9.2g/dl, the reticulocyte count was 17.5%, the platelets were 32 × 10^9/1, the peripheral smear showed marked fragmentation of the red cells. She was alert on admission but had another transient episode of hemiparesis shortly thereafter.

Laboratory tests can be seen in Table I. The patient was treated with 100 mg of prednisone and underwent a splenectomy on the second hospital day. The platelet count rose to 80 × 10^9/1 within 3 days and 104 × 10^9/1 within 5 days. The prednisone was tapered slowly over the next 5 days. Pathologically the spleen showed hyalin thrombi of the arterioles compatible with the diagnosis of TTP.

Second admission. The patient remained well until October 1966 when she developed a sore throat for which she received no medication. At that time, she noted some bruising. Her platelet count was found to be 90 × 10^9/1. She was treated with 60 mg of prednisone daily. Two days later she developed gross hematuria and was readmitted to Mount Sinai Hospital.

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Laboratory tests can be seen in Table I. The urinalysis showed many RBC's and proteinuria. The prednisone was increased to 200 mg a day. Initially the hematocrit dropped from 35% to 32% and the platelet count to 11 × $10^9/1$. After one week of therapy the patient responded with a rise in the platelet count and hematocrit. The prednisone was rapidly decreased to 100 mg a day and then slowly tapered over the next 5 months.

Third admission. The patient remained well until the following year—November of 1967 when she noted gross hematuria and was admitted to Mount Sinai Hospital.

Laboratory tests are shown in Table I. The patient was initially treated with prednisone 150 mg a day but this was increased to 200 mg a day because the hematocrit dropped from 38% to 24% and the platelets to 21 × $10^9/1$. After the increase in prednisone there was a prompt response and the prednisone was then rapidly decreased to 100 mg and then slowly tapered over the next 5 months.

Fourth admission. The patient remained entirely well, being seen at least once a year until March of 1975 when she had an upper respiratory infection for which she did not take any medications. One week later she developed gross hematuria and was admitted to Mount Sinai Hospital for the fourth time.

Laboratory tests showed the hemoglobin to be 12g/dl, hematocrit 35%, platelets 21 × $10^9/1$ and reticulocytes 8.6%. The peripheral smear showed fragmentation of the red cells (Table I). The patient was treated initially with prednisone 100 mg a day and this was increased to 150 mg a day when there was a drop in the hematocrit from 35% to 32% and platelets from 86 to 21 × $10^9/1$. There was a prompt response and the prednisone was rapidly decreased to 100 mg a day and the patient was discharged.

Fifth admission. One week after discharge from the hospital on 75 mg of prednisone she developed weakness of her left hand and was readmitted.

The patient was seen in consultation by a neurologist who felt she had a right encephalopathy presumably secondary to TTP.

The prednisone was increased to 200 mg a day and the patient was started on average molecular weight dextran (70,000) 500 ml intravenously twice a day for 10 days. The patient's neurological status improved within 2–3 days. The prednisone was decreased to 100 mg over 14 days and then slowly tapered over the next 5 months and stopped on 8-18-75. At this time her hemoglobin was 12.4 g/dl and platelets 462 × $10^9/1$.

Sixth admission. Four days after the prednisone was stopped the patient noted ecchymoses over her extremities and dark urine. There were no abnormal neurologic findings. The patient was noted to be hypertensive—blood pressure 154/104 at this time.

Laboratory examinations showed her hemoglobin to be 9.0 g/dl, hematocrit 27%, platelets 15 × $10^9/1$ and reticulocytes 10.2%. Peripheral smear showed fragmentation of the red cells (See Table I).

The patient was treated with prednisone 180 mg a day. She was given average molecular weight dextran 500 ml twice a day for 14 days. The patient responded promptly to this therapy. The prednisone was rapidly decreased to 100 mg and then tapered over the next 6 months to 5 mg of prednisone. She is being maintained on 5 mg of prednisone, and her blood counts have returned to normal levels. The hypertension has persisted. The patient has developed proctitis for which she received hydrocortisone by suppository. At the present time patient is completely well and is being maintained on 5 mg prednisone.

Results

Figure 1 summarizes the patient's course. The initial treatment was splenectomy and corticosteroids. The first and second relapses were treated successfully with corticosteroids. The fourth and fifth relapses were treated with corticosteroids and average molecular weight dextran.

Table I summarizes the laboratory data at diagnosis and at the times of each relapse on this patient. Hemolytic anemia, thrombocytopenia, red cell fragmentation and hematuria were present at diagnosis and at each relapse.

Table II summarizes the coagulation tests performed on the patient. A shortened partial thromboplastin time was found at the third, fourth, fifth and sixth admissions. A low fibrinogen was found on the fourth and fifth admissions. Fibrin split products were absent at the times the low fibrinogens were reported.

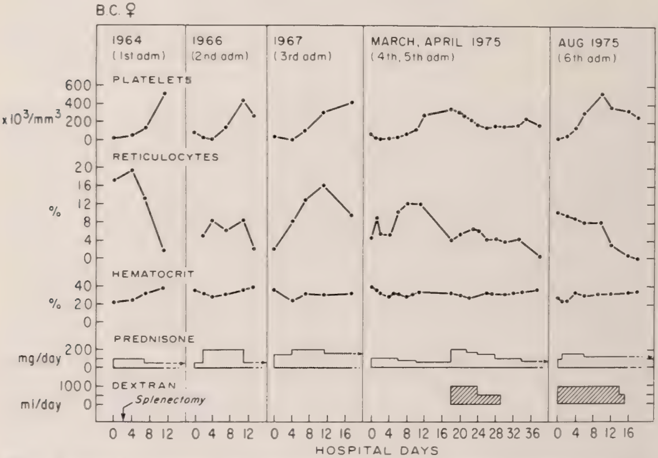

FIG. 1. Summary of treatment and response of patient during 6 hospital admissions for TTP.

TABLE I

Laboratory Examinations at Diagnosis and at Each Relapse

Admission to hospital	Date	HgB g/dl	Retic %	Platelet $\times 10^9$/l	RBC fragmentation	RBC's in urine	BUN mg/100 ml	Bilirubin lmg/100 ml	Haptoglobin mg/100 ml
1st	11/23/64	9.2	17.5	32	++++	+++	34	2.2	12
	11/18/65	13.0	2.1	480	0	0	14	0.6	132
2nd	10/27/66	8.7	8.4	11	+++	++	22	9.8	
	12/06/66	12.8	2.0	298	0	0	16	0.7	
3rd	11/03/67	7.5	8.1	21	++	++	32	2.5	200
	7/15/68	12.6	1.6	356	0	0	15	0.3	132
	9/08/69	13.8	2.0	418	0	0	17	0.4	232
	11/02/70	13.0	1.9	304	0	0	7		
	11/01/71	13.2	2.2	438	0	0			
	8/15/72	14.0	2.0	488	0	0			
	10/15/73	13.4	3.7	533	0		17	0.4	
	11/18/74	14.0	2.9	406	0		12	0.3	
4th	3/28/75	12.0	8.6	21	++	++		2.6	12
5th	4/29/75	11.2	12.1	296	+	0			
	8/18/75	12.4	2.7	462	+	0			
6th	8/25/75	9.0	10.5	15	++	+	28	3.3	
	12/29/75	14.2	2.8	509	0	0		0.4	200
	12/08/76	14.0	1.5	508	0	0		0.2	180

TABLE II

Serial Coagulation Tests

Admission to Hospital	Date	PT* Patient/ Control	PT** Patient/ Control	Fibrinogen mg/100 ml	FDP***	Factor VIII (%)	Factor IX
1st	11/23/64	12.5/14.2		320			
2nd	10/27/66	13.9/15.7	63/60	385			
	10/28/66			310			
	10/31/66			315			
3rd	11/03/67		43/60	330		150	
	11/06/67		40.5/51	250		140	
	9/09/68	12.5/12					
	10/14/69	12.4/12	38/50.6	275		111	90
	11/18/74	11/13	51/49	275			
4th	3/28/75	16.6/12	45/50	50	Neg		
5th	4/29/75	13.4/13	51/50	125	Neg		
	6/30/75	12.6/12	47/53	250			
6th	8/25/75		45/50				
	10/20/75	13/13	45/50	212			
	1/12/76	13.0/12.8	47/49	365			
	4/26/76	12/12	48/47	300	Neg		
	8/30/76	12/12.8	51/49	275			

* Prothrombin Time in seconds

** Partial thromboplastin time in seconds

***Fibrin degradation products (Thrombo Wellcotest)

Discussion

The patient reported here presented in 1964 with a typical history and findings of TTP. She improved after splenectomy and corticosteroids. She had 2 further exacerbations of the disease 2 and 3 years respectively after the original diagnosis was made. She then remained well for 8 years when she again relapsed and though she responded to treatment with corticosteroids and average molecular weight dextran infusions, she relapsed within one week of the prednisone being stopped, but again responded to steroids and dextran.

Most patients with TTP have an acute course. They usually recover or die within several weeks time. There have been reported patients who have a long prodromal illness prior to the diagnosis becoming obvious (2, 3).

There have also been rare patients with TTP who continue to show evidence of activity of disease (4, 5). Some patients are initially free of disease activity for periods of months to years before exacerbation of the disease occurs (6).

Table III shows eight patients reported in the literature with what appears to be chronic TTP plus the present case. Corticosteroids and splenectomy are the commonest treatment of this disease. Corticosteroids were given to 8 of the 9 patients. Six of the nine had a splenectomy performed. Three patients received heparin. There was no response in one patient, platelet count rise was seen in another but treatment had to be stopped because of bleeding, a third patient responded. Average molecular weight dextran was given to our patient because of our past favorable experience with this drug in TTP (7). Dipyridamole was given to two patients. One had an excellent response and the other did not respond. Cytotoxic agents 6-mercaptopurine and cyclophosphamide were given to 3 of the reported patients without apparent benefit.

TABLE III

Reported Cases of Chronic TTP.

Authors	Age/Sex	Survival Since Diagnosis Years	Treatment	Outcome
Present Case	35/F	12.1+	1) At diagnosis splenectomy prednisone—6 months 2) At first relapse two years after diagnosis prednisone—6 months 3) 2nd relapse 3 years after diagnosis prednisone—6 months 4) 3rd relapse 10.2 years after diagnosis prednisone—6 months Dextran 70—10 days 5) 4th relapse 10.10 years after diagnosis prednisone—6+ months Dextran 70—10 days	Alive with no definable evidence of disease
Golenfarb, P.B.[4] Finch, S.C.	40/F	10.5+	1) At diagnosis initially heparin—3 weeks inferior vera cava ligation Dexamethasone—16 weeks splenectomy 2) 6—mercaptopurine—6 weeks	Alive with active disease
Howard, D.J.[6] Robert, A.B. Page, F.T.	28/M	12+	1) At diagnosis initially prednisone—2-3 months splenectomy 2) 12 years later heparin dipyridamole—2 months	Alive with no evidence of disease
Wallace, D.C.[2]	5/M	5	1) At diagnosis Transfusion At relapse 3½ years later—treatment not specified and patient died in 6 days	Died—At autopsy—typical lesions of TTP were found in myocardium, liver, kidneys, and gastrointestinal tract.

Distenfeld, A.[12] Oppenheim, B.	55/M	10 months	1) At diagnosis hydrocortisone—2 weeks hydroxychloroquine splenectomy triamcinolone—2 months 2) At relapse—10 months later steroids—died in 7 days.	Died At autopsy Thrombi in arteroiles in heart, liver, kidneys, pancreas, brain, lymph nodes.
Bernard, R.P.[3] Bauman, A.W. schwartz, M.D.	7/F	6.8	1) Steroids transfusion splenectomy 2) At relapse 7–8 months later treatment not specified 3) At relapse 82 months 2nd recurrence treatment not specified died in 4 days	Died at autopsy thrombi, brain, heart, adrenal, kidneys, and lymph nodes.
Fiddes, P.J.[5] Penny, R.	68/M	7 months +	1) At diagnosis prednisone—3 weeks 2) At relapse 3 months later prednisone Approx 1 month heparin—Approx. 6 weeks warfarin sodium	Alive with evidence of disease
Wallace, D.C.[2] Lovric, A. Clubb, J.S. Carseldena, D.B.	10/M	8	1) At diagnosis—penicillin at first relapse 3 years later transfusion prednisone 5 months splenectomy dypyridamole Heparin Cyclophosphamide	Died at autopsy thrombi in kidney, heart, and gastrointestinal tract

One patient reported by Howard, et al (6) had TTP treated by corticosteroids and splenectomy. Patient, then was lost to follow up but was apparently well until 12 years later when he developed a recurrence of disease after an influenza like illness (6). He responded to treatment with dipyridamole. Both this patient and the patient reported here had periods of several years during which they were apparently well until they developed upper respiratory infections as a prodrome to exacerbation of TTP.

The etiology of TTP is unknown. An infectious agent has been postulated but not proven. Several cases of TTP have been reported in which the patient had an infection prior to onset of TTP. A case report of 2 sisters dying of TTP within several months of one another has been reported (8). A case of a husband and wife succumbing to this disease within a short period of time has also been reported (9). In the patient reported here several coagulation studies over the years have failed to reveal any conclusive evidence of disseminated intravascular coagulation. Disseminated intravascular platelet aggregation has been found in some patients with TTP (10, 11). Certain viral illnesses have been associated with thrombocytopenia. Perhaps the viral illness acted as a triggering mechanism in these susceptible hosts.

Five of the nine patients with chronic TTP have died—most within one to two weeks of relapse. In 2 of these patients the treatment at the time of first relapse was not specified. The other 3 patients received corticosteroids. One patient received heparin and dipyridamole without response.

Three of the four surviving patients have evidence of active disease. Two are on treatment; one with coumadin and the other with prednisone. The case reported here is unusual in having 4 relapses in 12 years since the diagnosis, with periods of time ranging from 6 months to 7 years when she was completely disease free and off of all therapy. That she is exquisitively sensitive to corticosteroids was seen when her last relapse occurred one week after the prednisone (5 mg) was stopped.

Two of the four surviving cases have had continuously active disease since diagnosis. The patient, reported by Howard (6) et al, relapsed 12 years later after an influenza-like illness. Our patient relapsed 3 times after an upper respiratory infection. Immunoelectrophoresis on our patient shows that she had hypogammaglobulinemia when tested at time of her first relapse (IgG 0.72 g/dl) and this value returned towards normal levels at time of quiescence of her disease. The therapy of patients who relapse from TTP is as controversial as the therapy at the time of diagnosis. It would appear that agents that interfere with platelet aggregation either dextran or dipyridamole with or without corticosteroids are the treatment of choice at this time.

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Student Section

Postoperative Complications of Colon Surgery

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During a five week period in 1977 an investigation of 44 consecutive patients admitted for elective colon surgery was carried out in the Mount Sinai Hospital. The goals of the study were to:

1. determine the incidence of wound infection and anastomotic leakage,
2. compare the characteristics of the patient populations with and without postoperative complications of wound infection and anastomotic leakage,
3. study the use of prophylactic antibiotics by the surgical staff of The Mount Sinai Hospital.
4. analyze the financial implications of the investigation.

Design

The study included 44 consecutive patients having elective surgical procedures on the colon during a five-week period in June and July of 1977 at The Mount Sinai Hospital. Excluded from the study were all patients with emergency operations; one patient with squamous cell carcinoma of the perineum who required a bilateral groin resection, vulvectomy, hysterectomy and bilateral salpingo oophorectomy; and another patient whose medical record could not be located. Charts of the 44 patients were reviewed and the patients' age, sex, pertinent medical history, diagnosis, bowel preparation preoperatively, duration and type of operation, method of wound closure, preoperative and postoperative hospitalization duration, drugs administered, and temperature variation were noted. The criteria for wound infection was purulent drainage from the wound. Feces draining from the wound constituted anastomotic leakage. For the purposes of the study, any patient without wound infection or anastomotic leakage was considered to be free of postoperative complications.

Results

Of the 44 patients, 42 returned home; one patient with a 3-year history of renal failure remained in the hospital; and an 89-year-old male who had a colostomy performed during the course of the study period died of renal failure, cardiogenic failure and pulmonary insufficiency subsequent to having an anterior resection of the colon.

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There were 9 postoperative complications, 7 wound infections and 2 anastomotic leakages. Two patients who later developed wound infections had contaminated operative fields due to diverticula perforation and resulting abcess formation. Both infections were discovered prior to the fourth postoperative day when non-streptococcal wound infections usually manifest. Cultrues taken in 4 of the 7 infections and in 1 of the 2 leakages grew enteric bacteria. 8 of the 9 patients who developed postoperative complications received prophylactic antibiotics (Table I).

More males than females had surgery on the colon. The average age of the patients developing postoperative complications (64) was greater than that of the patients who developed no wound infection or anastomotic leakage (60). The duration of the average preoperative (12 days) and postoperative (19 days) hospital stay was greater in the patient with postoperative complications as opposed to the preoperative (9 days) and postoperative (15 days) hospital stay in the patient with no complications (Table II).

The category of "Inflammatory Disease" includes diverticulitis, Crohn's disease, and ulcerative colitis. Any patient found to have diverticular disease or villous adenoma in addition to infiltrating carcinoma was classified in the

TABLE I

Wound Infections

Procedure	Diagnosis	Antibiotics		Packing	Drains	Culture
		Preop.	Postop.			
Closure Colostomy	Cancer	–	Keflin	+	+	Proteus mirabili E Coli Enterococcus Actinobacter
Closure Colostomy	Cancer	Keflin	Keflin	+	–	–
Anterior Resection	Villous Adenoma	Keflin	Keflin	–	+	E Coli
Anterior Resection	Cancer	–	–	–	+	Klebsiella Staph. epiderm.
Anterior Resection + Colostomy	Cancer	–	Kefzol	–	–	–
Sigmoid Resection	Divertic.	–	Keflin	+	+	–
Sigmoid Resection + Colostomy	Divertic.	–	Kefzol	+	+	Proteus E Coli Enterococcus
Anastomotic Leakage						
Closure Colostomy	Cancer	–	Kefzol	–	+	–
Anterior Resection + Colostomy	Cancer	–	–	–	+	Proteus E Coli

TABLE II

	Male	Female	Age	Preoperative stay	Operative duration	Postoperative stay
Complicat.	56%	44%	64	12 days	2.13 hours	19 days
No Complicat.	60%	39%	60	9 days	3.40 hours	15 days*

* This figure does not include the patient who died nor the patient still in the hospital.

TABLE III

Diagnosis

	Cancer	Lymphoma	Inflammatory disease	Villous adenoma
Total No.	32	1	8	3
Percent Complic.	19%	0	25%	33%

TABLE IV

Operative Procedures

Procedure	Number	Contaminated field	Wound infection	Anastomotic leakage
Segmental Resec. Hemicolectomy Subtotal Colec. Ileocolic Resec. with Anastomosis	21	1	1	0
Segmental Resec. Hemicolectomy with Caecostomy or Colostomy	5	1	1	0
Anterior Resec. with Anastomosis	8	0	2	0
Anterior Resec. with Caecostomy or Colostomy	4	0	1	1
Anterior Posterior Resec. with Colostomy	1	0	0	0
Proctocolectomy with Ileostomy	2	0	0	0
Colostomy	1	0	0	0
Closure Colostomy	3	0	2	1

latter category. 73% of the patients had cancer. Of these, 6 (19%) developed postoperative complications as compared to 1 patient (33%) with villous adenoma and 2 patients (25%) with inflammatory bowel disease. (Table III).

Table IV is a classification of the operative procedures. One patient was listed in two different categories having had a hemicolectomy and anterior resection. Another patient underwent an anterior resection and anastomosis with a preexisting colostomy. 100% (3) of patients with closure of colostomy developed postoperative complications as opposed to 50% (2) of those with anterior resection and cecostomy or colostomy, 25% (2) of anterior resection and anastomosis, 20% (1) of resection and cecostomy or colostomy, and 5% (1) of resection and anastomosis.

Sump or Penrose drains were used and wounds were packed with iodoform or plain gauze. (Table V).

TABLE V

Wound Closure

	Packing	Drains	Both	Neither
Total No.	3	17	21	3
No. with Complic.	1	4	4	0

TABLE VI

Surgeon

	Surgeon				
	A	B	C	D	E
No. Cases	1	1	1	4	7
No. Complic.	1	1	1	2	4

TABLE VII

Antibiotics

Wound Infections	Number of patients	Neomycin	Preop.	Antibiotics	
				During	Postop.
0	6	+	−	−	−
2	3	−	−	−	−
0	4	+	+	*	−
0	0	−	+	−	−
0	2	+	+	+	−
0	0	−	+	+	−
2	7	+	+	−	+
0	1	−	+	−	+
0	2	+	−	+	+
0	1	−	−	+	+
0	13	+	−	−	+
3	5	−	−	−	+

The case load for each of the 22 attendings who performed the surgical procedures ranged from 1 to 9 patients. Patients of 5 attending surgeons developed postoperative complications. (Table VI).

All patients received a bowel preparation preoperatively consisting of chemical and/or mechanical cleansing and dietary restriction or low residue diet, liquid or no food. 38 patients also received oral neomycin 1 gram q1h × 4, then 1 gram q4h from 1 to 4 days preoperatively as part of the preparation, oral erythromycin was added to the neomycin in one case.

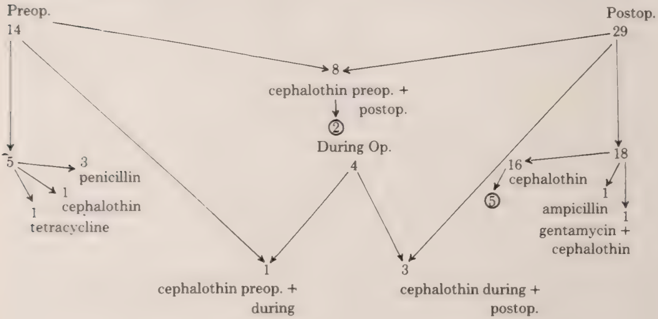
Tables VII and VIII relate the incidence of postoperative complications to the administration of specific antibiotics used prophylactically or in the bowel preparation. In the majority of cases, antibiotics were begun the day preceding or the day of the operation.

Discussion

The rate of wound infection after colonic surgery has been reported in the literature to range from 2.1% (1) to 61% (2) depending on the institution and stringency of the criteria. The criteria for wound infection in this study was purulent drainage from the wound, yielding an infection rate of 16%. The rate

TABLE VIII

Specific Anttibiotics


Preop.
14
Postop.
29
8
cephalothin preop. + postop.
②
During Op.
4
5
3
penicillin
1
cephalothin
1
tetracycline
18
16
cephalothin
⑤
1
ampicillin
1
gentamycin + cephalothin
1
cephalothin preop. + during
3
cephalothin during + postop.

Red arrow indicates wound infection

of anastomotic leakage has been reported as ranging from 5–10% (3, 4) to 51% (5) as compared to our rate of 6%.

Progressive incidence of wound infection and anastomotic leakage was associated with increasing age of the patient as previously documented in other studies (6).

The longer the preoperative hospital stay, the greater the rate of postoperative complications. With increased time in the hospital environment the patient becomes exposed to sources of nosocomial infection. However, it is possible that it is the "sicker" patient, who is already more likely to develop a postoperative complication due to depressed immune responses, who requires a longer preoperative stay.

Other studies have shown the number of wound infections to increase with increased operative duration (7). This is logical because the majority of wound infections result from contamination in the operating room. With increased operative duration, there is also increased chance of bacterial contamination. Because of the small size of this study, the data obtained were deceiving. Three closure colostomy procedures resulted in complications. The average operative duration in the complicated case was thus skewed due to the relative brevity of the procedure.

In addition, the importance of bacterial contamination intraoperatively is underscored by the fact that both patients that had contaminated operative fields developed wound infections.

No conclusions could be drawn from the data on the method of wound closure. Drains permit the egress of fluid as well as allowing ingress of bacteria. One must recall that it is the wound with increased liklihood of developing fluid accumulation and infection that requires drainage. Thus, it is probable that rather than increasing the rate of infection, drainage decreased the severity of an infection destined to develop.

Each of the 3 patients who required a closure of their colostomy, a highly contaminating procedure, developed postoperative wound complication. The skill of the surgeon is an important factor in reducing the rate of wound infection by avoiding excessive trauma to tissues, the abuse of electrocautery or ligatures, and in insuring adherence to sterile technique (8). The rate of anastomotic leakage can further be reduced by allowing proximal decompression and eliminating distal obstruction of the bowel. Surgical skill is related to experience as evidenced by the fact that 3 surgeons performed only 1 colonic procedure and had 1 postoperative complication in contrast to a more experienced surgeon who performed 9 procedures with no complications.

Although mechanical cleansing of the colon has been found to be the most important single element in bowel preparation, neomycin was effective in further decreasing the number of microorganisms in the gut (9). The bacterial flora of the colon contains predominately E Coli and Bacteroides fragilis as well as clostridia, streptococci and other aerobic coliforms.

Parenteral antibiotics have been found to be useful in reducing the incidence of wound infection in colonic surgery. An effective regimen consists of the acheivement of an adequate blood level of the antibiotic at the time of surgical incision in order to increase defenses against bacterial invasion (10). Penicillin (11), cephaloridine (12), gentamycin and lincomycin (13), have all been reported to decrease the incidence of wound infection. Studies have shown that there is no justification for administering prophylactic postoperative antibiotics because of insufficient blood level at time of contamination. Yet, 68% of patients received postoperative antibiotics introducing the chance of increased morbidity due to side effects as well as incurring unnecessary financial expenditures.

A study done at Duke University Medical Center showed "64% of total antibiotic therapy was not indicated or inappropriately administered in terms of drugs and dosages" (14). Continuing education of physicians as to proper use of antibiotics as well as a system of monitoring antibiotic administration may be warranted.

The problem of postoperative complications is an important one due to the ethical as well as financial considerations involved. It is estimated that a postoperative day in the hospital costs $220. The patient with postoperative complications spends an average of 4 additional days in the hospital and thus incurs $880 of additional charges. Increase in duration of hospital stay results in a tremendous financial burden by the loss of work time and the increased expense of prolonged hospitilization. In this era of rapidly increasing medical costs, it is interesting to note that by using good medical and surgical technique to treat the patient in an effort to decrease postoperative complication, the doctor can concurrently decrease unnecessary expenditures and treat the "ills" of the hospital.

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Myositis and Collagen Disease: A Muscle Biopsy Study

PETER PICKENS, Sc.B.

Introduction

The inflammatory myopathies (e.g., polymyositis, myositis associated with "collagen disease") remain one of the most diagnostically and therapeutically difficult groups of diseases because of their obscure pathogenesis. A qualitative analysis of muscle biopsies was therefore carried out to determine whether patterns of histopathology could be correlated with patterns of clinical disease. The analysis included all muscle biopsies with diffuse myositis that have been received during the last ten years. The study also attempted to determine whether specific histologic changes on muscle biopsy could be related to currently popular theories of the pathogenesis of these clinical syndromes, and, if so, the extent to which these changes are peculiar to that disease.

Materials and Methods

Muscle biopsies were obtained from prospectively studied patients with a variety of neurologic, neuromuscular, and systemic diseases according to a previously published report (1). Of nearly 1300 muscle biopsies examined during the period from 1966–1976, 115 were classified histologically as myositis, a term used in this report to indicate the presence of inflammatory cells in the microscopic examination of the muscle biopsies. These were further divided into three categories: a) vasculitis as the predominant pathologic change; b) focal or multifocal perivascular aggregates of inflammatory cells; and c) diffuse, infiltrating inflammation with extensive areas of muscle cell necrosis, (Fig. 1). The last group consisted of nineteen biopsies. These biopsies were reexamined without knowledge of the corresponding clinical diagnosis. The corresponding clinical diagnoses were then grouped under the categories of histologic abnormalities evident on microscopic examination. These categories included:

Inflammation within the vessel wall, i.e., vasculitis or arteritis (Fig. 2).
Interstitial inflammation (Fig. 3).
Infiltrating inflammation into the endomysium.
Perivascular cuffing of inflammatory cells (Fig. 4).
Associated changes in muscle fibers:

1. necrosis.
2. basophilia.
3. random angulated fibers, e.g., "neurogenic atrophy" (Fig. 5).
4. regional atrophy with increase in endomysial connective tissue.
    a) large groups (Fig. 6).
    b) small groups.

From Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

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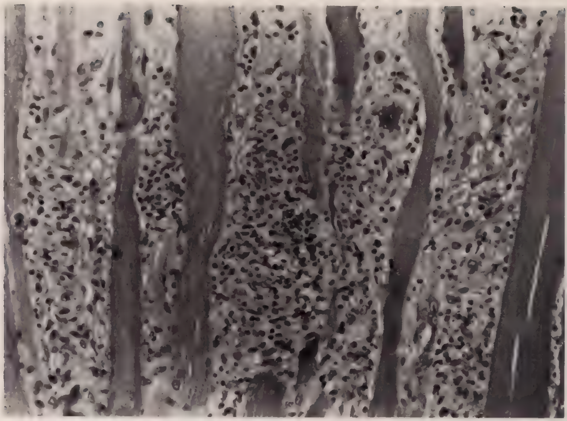

FIG. 1. Characteristic histologic changes of diffuse myositis: extensive infiltration of mononuclear inflammatory cells with necrosis and phagocytosis of muscle fibers (longitudinal section).

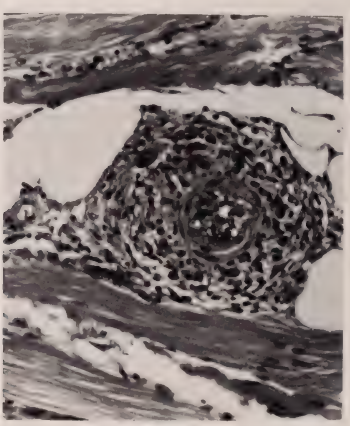

FIG. 2. Vasculitis occurring in a patient from the SLE-RA-PN group (cross-section).

The associated clinical diagnosis represents the diagnosis upon discharge from the hospital, as stated in the hospital chart. The clinical diagnoses corresponding to the nineteen biopsies under analysis are listed in Table I.

The case diagnosed as "myopathy" was excluded from the study because the clinical data was unavailable. Although polymyositis and dermatomyositis

TABLE I

Clinical Diagnosis of 19 Patients with Diffuse Myositis on Muscle Biopsy

Polymyositis (P)	8
Dermatomyositis (D)	2
Systemic Lupus Erythematosus (SLE)	3
Rheumatoid Arthritis (RA)	2
Periarteritis Nodosa (PN)	2
Scleroderma (SCL)	1
"Myopathy"	1

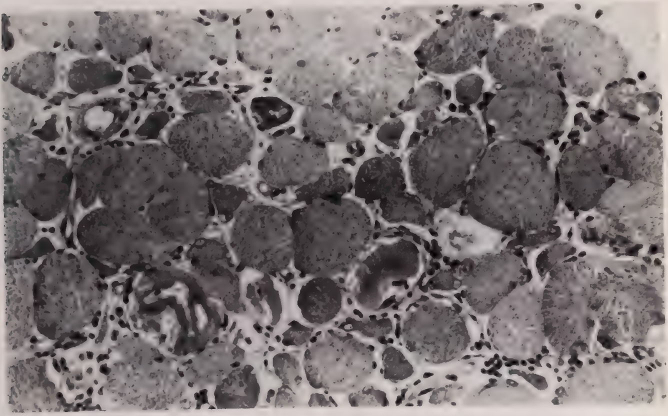

FIG. 3. Predominantly interstitial infiltration of inflammatory cells.

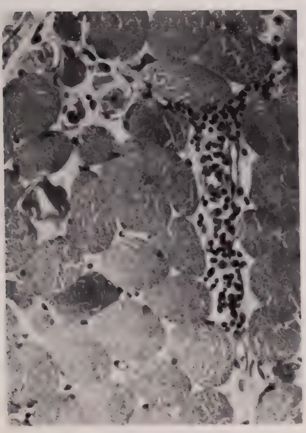

FIG. 4. Mononuclear cells distributed around a central vessel, so-called "perivascular cuffing."

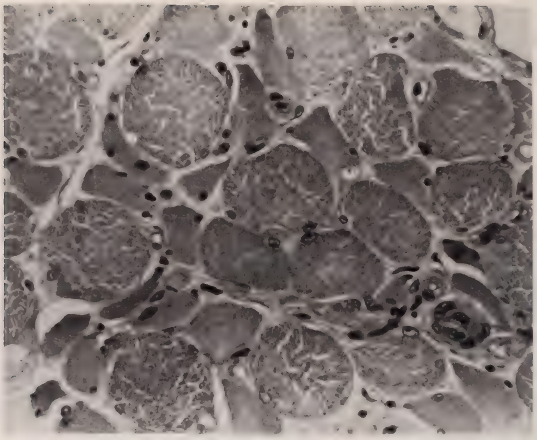

FIG. 5. Randomly distributed angulated, atrophic fibers, constituting a neurogenic atrophy pattern.

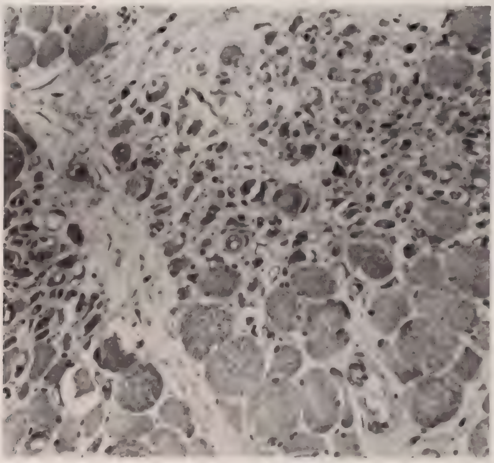

FIG. 6. A large group of atrophic fibers with increased endomysial connective tissue between fibers.

are considered to be separate diseases by some investigators, for the purpose of this study they are combined into one group termed polymyositis-dermatomyositis (P-D), consisting of 10 patients. The symptoms and signs on physical examination, the results of laboratory tests, and the information provided by muscle biopsy analysis were utilized by the patients' physicians in formulating the clinical diagnosis.

Results

The results of the microscopic analysis of the 18 muscle biopsies in our sample are presented in Table II. Shown is the number of muscle biopsies in each clinical syndrome group illustrating the specific histological change. The numbers in parentheses indicate patient identification within each disease group.

We have separated the clinical syndromes represented here into P-D versus a composite category of SLE, RA, and PN, which is reasonable in view of current theories of the pathogenesis of these diseases, a concept which will be expanded later. Under this concept, four of five patients who showed evidence of vasculitis were suffering either from SLE, RA, or PN (80%), while only one was from the P-D group. Hence, four out of seven patients (57%) in the SLE-RA-PN group showed evidence of vasculitis, while only one of the ten patients (10%) with P-D showed such features. All four patients showing vasculitis from the SLE-RA-PN group also presented patterns of neurogenic atrophy. Further, five of the six patients revealing patterns of neurogenic atrophy correlated with the clinical diagnosis of the SLE-RA-PN group, and four of these five patients simultaneously showed evidence of vasculitis.

In assessing the reliability of muscle biopsy analysis in suggesting a clinical diagnosis in the presence of diffuse myositis, the presence of both vasculitis and patterns of neurogenic atrophy were found in four patients, all of whom suffered either from SLE, RA, or PN. These two histopathologic changes were uncommon in the P-D group, each appearing only once, and not in the same patient. The association of vasculitis and neurogenic atrophy both independently and as concomitant findings with the SLE-RA-PN group is statistically significant, ($p < .05$).

Interstitial inflammation was observed in four patients, all of whom suffered from P-D. This association is statistically significant, ($p < .05$).

Focal perivascular accumulations of inflammatory cells was a non-specific finding in this study, having been identified in seven patients with P-D, two with SLE, one with RA, and one with PN. Similarly, evidence of fiber necrosis, basophilic fibers, and both large and small regions of atrophic fibers with increased endomysial connective tissue did not correlate preferentially with any of the diseases under study.

A comparison of the symptomatology and relevant lab data at initial presentation in the two groups under consideration, P-D and SLE-RA-PN, reveals somewhat distinct findings. Patients in the P-D group characteristically complained of symptoms rooted in a myopathic process. Of the seven P-D patients

TABLE II

Correlation of Pathology with Clinical Diagnosis

1. Patterns of Inflammation

	Vasculitis	Infiltrating inflammation	Interstitial inflammation	Perivasc. cuffing	Fiber necrosis
SLE (n = 3)	1(#3)	1(#3)	–0–	2(#1, 3)	all
RA (n = 2)	1(#1)	2(#1, 2)	–0–	(#1)	all
PN (n = 2)	2(#1, 2)	1(#2)	–0–	1(#1)	all
P-D (n = 10)	1(#9)	7(#1, 2, 3, 4, 6, 7, 9)	4(#5, 8, 9, 10)	7(#1, 2, 6, 7, 8, 9, 10)	8(#1, 3, 4, 5, 6, 7, 9, 10)
SCL (n = 1)	–0–	1(#1)	–0–	–0–	all

2. Changes in Muscle Fibers

	Basophilic fibers	Neurogenic atrophy	Regional atrophy with fibrosis		Connective tissue increase
			Large group	Small group	
SLE (n = 3)	3(#1, 2, 3)	2(#2, 3)	1(#3)	1(#2)	3(#1, 2, 3)
RA (n = 2)	1(#1)	1(#1)	1(#1)	–0–	1(#1)
PN (n = 2)	2(#1, 2)	2(#1, 2)	1(#2)	–0–	2(#1, 2)
P-D (n = 10)	5(#1, 2, 4, 9, 10)	1(#7)	–0–	4(#2, 4, 7, 10)	5(#1, 5, 7, 8, 9)
SCL (n = 1)	1(#1)	–0–	–0–	1(#1)	–0–

for whom this data was available, five had experienced muscle pain, four had had tenderness, and all patients had experienced weakness, (three had had only proximal weakness, while in four proximal weakness had exceeded distal weakness). The only muscle complaint worthy of note in the SLE-RA-PN group was the appearance of weakness in four of the six patients for whom this data was available, which also showed more proximal involvement. In the SLE-RA-PN group, typical initial manifestations of disease included joint swelling (four patients), arthralgias (four patients), and joint stiffness (three patients). Raynaud's syndrome associated primarily with the SLE-RA-PN group, which accounted for four of the five observed cases. Dysphagia was observed in four patients, all of whom were diagnostically placed in the P-D category.

Elevations of CPK, SGOT, and SGPT were observed in most P-D patients at presentation. Elevated ESR was observed in virtually all patients. Antinuclear antibody was positive in two patients in the SLE-RA-PN group: one with RA and one with SLE. In the two remaining SLE patients, no information regarding status of ANA was obtainable. The only example of positive ANA in the P-D group was one patient who had complained of arthritis, but who lacked evidence of vasculitis on muscle biopsy. Three patients in the SLE-RA-PN group and one patient in the P-D group had documented positive latex fixation test. Positive L.E. prep was observed in three cases: one patient with RA, one with SLE, and one with P-D.

In eight of the 18 patients involved in this study, myositis occurred in the course of one of the other collagen-vascular diseases, therefore constituting an "overlap syndrome," as defined by Bohan and Peter (2). Our findings that frank arthritis, arthralgias, or Raynaud's syndrome more accurately typify the presenting manifestations of the SLE-RA-PN or "overlap" group and not true

P-D is in general agreement with their data in this regard. The universal complaint of muscle weakness in our P-D patients is in agreement with Bohan et al's survey, in which 92% of their P-D patients had complained initially of weakness. However, we observed muscle pain in more than 50% of our P-D patients, while in their experience only 25% had complained of myalgias. In fact, their study revealed a higher incidence of myalgias in the "overlap" group (41%) as compared to the P-D group (25%). In our "overlap" group, two out of six had complained of myalgias.

Discussion

Within the framework of this report, we have postulated that different pathogenetic mechanisms may exist among the diseases represented here (SLE, RA, PN, P-D, and SCL) and that this diversity may be reflected in disease-specific changes on muscle biopsy. Our biopsy findings suggest, however, that neither the severity of inflammation nor specific histopathologic changes are adequate to reliably differentiate between these diseases. Nevertheless, the presence of vasculitis seems to be a valuable criterion in distinguishing those diseases with a presumed immune-complex basis (SLE, RA, PN) from those without (P-D). The statistical association of neurogenic patterns of atrophy with the SLE-RA-PN group supports the concept that these diseases are primarily vasculopathic, and therefore nerves as well as muscle can be the target of the disease process.

Substantial evidence has been accumulated which supports the concept that deposition of immune-complexes in vessel walls with resultant vasculitis is essential in the development of lesions in SLE, RA, and PN. With regard to SLE, support for immune-complex deposition as a pathogenetic mechanism has been suggested by Koffler et al (3), who demonstrated in the kidney that the progressive deposition of immunoglobulins and complement within the renal mesangium and then within the glomerular basement membrane correlated with the severity of renal disease. Fibrinoid necrosis of medium-sized renal arteries has been shown to be associated with immunoglobulins, complement, and DNA antigen within the vessel wall (4). Vasculitis involving small blood vessels appears to be associated with CNS disease in SLE. However, the question of whether immune-complex deposition is involved here has not been adequately challenged experimentally, and one immunofluorescent study of brain tissue from three patients with CNS lupus failed to demonstrate immunoglobulin deposition (5). Nevertheless, immune complexes have been demonstrated within the choroid plexus (6) and CSF (7) in patients with CNS involvement.

Paronetto (8) identified immunoglobulins, complement and fibrinogen in the inflamed small and/or medium-sized arteries of several patients with PN. The possibility that autologous antibody to vascular antigen might be the mediator of the inflammation was discounted by his demonstration that precipitation of soluble human artery antigen by serum from a patient with PN did not occur and the patient's serum, when labelled with fluorescein, failed to localize in either inflamed or normal blood vessels.

Considerable evidence is at hand which supports the concept that the necrotizing vasculitis of RA is immune-complex mediated. Necrotizing vasculitis occurs exclusively in patients with higher titers of rheumatoid factors, and a positive correlation has been demonstrated between the presence of rheumatoid factor in the serum and progression of the rheumatoid process (9). Finally, deposits of immunoglobulins, complement, and anti-IgG have been found in vessel walls (10).

In this report, four of seven biopsies corresponding to a clinical diagnosis of either SLE, RA or PN manifested evidence of vasculitis, whereas only one of the ten biopsies associated with P-D revealed this finding. We were unable to identify evidence of vascular inflammation in two of our three SLE patients and in one of our pair of RA patients. This is probably due to the infrequency with which vascular lesions in these diseases are identified on muscle biopsy. Sokoloff (11) was able to diagnose arteritis four times more frequently in 100 serial sections of muscle than in a single random section in RA. In this regard the known segmental nature of the vascular lesions in RA must be mentioned (12). He has also demonstrated the efficacy of serial sectioning of muscle biopsies in identifying evidence of arteritis in SLE (13).

The infrequency with which vasculitis and neurogenic patterns of atrophy were encountered in biopsies corresponding to clinically-diagnosed P-D possibly reflects the proposed myopathic and not vasculopathic basis of this disease. Manghani et al (14), in an experiment in which different rabbit muscle fractions were injected into guinea pigs, was able to induce two variants of polymyositis, both of which closely resembled pathological variants of the human disease. They demonstrated a strong correlation between the injection of either whole muscle homogenate or the myofibrillar fraction and the development of severe myonecrosis associated with an active infiltration by histiocytes, lymphocytes, plasma cells, and neutrophils. Injection of mitochondrial, microsomal, and the supernatant fractions produced no myonecrosis, but rather collections of lymphocytes and histiocytes lying in the connective tissue between fibers. Serological analysis revealed the persistence of high titers of anti-muscle antibody in those groups injected with whole muscle homogenate or myofibrillar fractions, but not with the other fractions. Manghani's interpretation of the development of interstitial inflammation in the absence of myonecrosis is that this pattern represents a hypersensitivity reaction developing in the region of the sarcolemma of insufficient severity to destroy the adjacent fibers.

Other investigators have postulated an aberration in cell mediated mechanisms in the pathogenesis of P-D. Johnson et al (15) demonstrated that muscle samples from 11 patients with P-D when incubated with autologous sera resulted in the production of lymphotoxin, a mediator of delayed hypersensitivity, in each case examined but not in controls. The capacity of the isolated lymphotoxin to destroy muscle cells was proven using fetal muscle monolayers as target cells.

The concept that the muscle fiber itself is a target of an aberrant immune apparatus in P-D is in keeping with the histopathologic changes seen on muscle biopsy. Of ten biopsies corresponding to clinically-diagnosed P-D, eight (80%) showed active fiber necrosis. However, all biopsy specimens corresponding to SLE, RA, PN, and SCL showed fiber necrosis as well; this finding is thus nonspecific and useless in distinguishing the presumed vasculopathic diseases from P-D or SCL.

Interestingly, evidence of interstitial inflammation was seen in four biopsies, all of which represented P-D. While this would seemingly support Manghani's contention that hypersensitivity may play a role in P-D (14), this support is undermined by the simultaneous presence of active fiber necrosis in three of these biopsies. Nevertheless, interstitial inflammation was not seen in the other diseases under consideration. However, in their lengthy analysis Walton and Adams demonstrated no difference in the frequency of interstitial inflammation on muscle biopsy in patients with polymyositis alone or in myositis associated with other collagen diseases (16).

Summary

We have attempted to identify histopathologic changes on muscle biopsy analysis that would be useful in differentiating the diffuse myositides associated with clinical syndromes of the collagen disease variety. The presence of vasculitis and compact aggregates of angulated, atrophic fibers (so-called neurogenic atrophy) associated exclusively with diseases in which immune-complexes presumably play a role: SLE, RA, and PN ($p < .05$). Evidence of interstitial inflammation was seen exclusively in biopsies corresponding with P-D, and this association was also significant at the 5% confidence level ($p < .05$). Perivascular accumulations of inflammatory cells and active fiber necrosis and regeneration, as well as other changes in fiber morphology, did not preferentially associate with any clinical syndrome. We conclude that the histopathology of diffuse myositis, when it occurs in the setting of an "overlap syndrome" such as myositis in SLE, RA, or PN, is distinguishable on muscle biopsy analysis from true poly-dermatomyositis.

Acknowledgments

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The Student's Corner

JONATHAN STEINBERG, B.A., Editor

This column is a forum for medical students to comment on issues concerning medical school and medical education. The editor of this column is a second-year medical student and elected student representative at Mount Sinai School of Medicine of The City University of New York. Mount Sinai School of Medicine students are invited to take advantage of this opportunity to reach a wide and influential readership. Medical students from other schools are also invited to contribute.

Contact Mr. Steinberg through Mount Sinai School of Medicine, The Annenberg Building, Room 13-98A, Fifth Avenue and 100 Street, New York, N. Y. 10029. If you do not have time to write an entire column, you still can contact Mr. Steinberg and share your thoughts on a particular topic which perhaps can be incorporated into a future column.

David A. Dreiling, M.D.
Editor-in-Chief

Preventive Medicine

Submitted by
ALEXANDER AMBROZ, B.S.*

Contemporary medical education is focused for the most part on the management of acute medical problems. Emphasis on prevention of disease is comparatively lacking. Thus, physicians often do not take basic steps to prevent serious consequences of many diseases. A recent DHEW study found that of the 198.2 million office visits in 1975, a blood pressure was taken in only 40% of them, even though it is well known that hypertension is one of the major killers of man. There is a definite need in the medical education curriculum for more extensive instruction on various methods by which many chronic diseases can be avoided.

The eradication or control of many infectious diseases is one of the triumphs of modern medicine. Smallpox, which at one time decimated populations, is all but extinct. New antibiotics are continually being developed to fight emerging strains of microorganisms. The result of these and other advances has been an increase in the lifespan of the average American from 30.7 years in 1900 to 71 years today. With this prolongation of life, however, new diseases have come into prominence. Against these chronic illnesses modern medicine is finding it hard to develop a "magic bullet." Therapies are usually supportive. As a possible consequence of this, the rate of increase in lifespan began to slow down about 20 years ago. It is increasingly being recognized that the best way to deal with a number of these noninfectious diseases is to prevent them.

It has been estimated that more than 50% of the population is obese. Although there is virtually no end to proposed therapies for this affliction it is believed that avoidance of overfeeding of infants is almost the only sure way of managing the problem.

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The work of Dr. Selikoff in associating asbestos with mesothelioma is a classic example of the type of work that needs to be done on a much broader scale. This tumor is virtually incurable, but without exposure to asbestos it is extremely rare. Nutrition is another area that needs to be more strongly emphasized in medical school. A letter in the *Journal of the American Medical Association* last year observed that only 19% of American medical schools had formal courses in nutrition. Yet the potential for disease prevention is considerable. Despite the considerable controversy over the recommendations of the American Heart Association on diet in the prevention of heart disease, recent data from the National Heart, Lung, and Blood Institute show that cardiovascular mortality has decreased from 369 deaths per 100,000 population in 1960 to 349.2 in 1974, a more than 5% decline.

Nevertheless, research in preventive medicine lags behind that done for acute illnesses. Few long-term studies exist comparing the value of different behaviors. An important project of this type was published in *Journal of the American Medical Association* about 20 years. The mortality and morbidity of Seventh Day Adventists, a religious sect that prohibits meat, smoking, and alcohol, was compared with that of the general population. The lower incidence of disease in this population was significant. Interest in this type of work is not great. As of 1975 there were a mere 6000 preventive medicine specialists out of a total population pool of 400,000.

The value of preventive medicine has been questioned by those who believe that it would depend too much on patient compliance which is not very reliable. Indeed, a recent study in the *New England Journal of Medicine* looked at the effects of educating people about the effects of hypertension and seeing how they would then comply with their medication. Surprisingly it was discovered that there was no difference in compliance. (However, there was no assessment of the β error, so that it is possible that a significant difference was not appreciated.)

It appears that the physician plays a predominant role in developing patient compliance. In advertisements from the American Cancer Society it was asserted that the physician's intervention is probably the deciding factor in whether or not a well-educated woman will examine her breasts despite millions of dollars of TV and other advertising. The medical profession also has a critical role in countering the enormous budgets liquor and cigarette manufacturers have for promoting their merchandise. In medical school there should be instruction on the best ways the physician can influence his patients to avoid habits that are detrimental to their health.

In the recent past the lack of emphasis on preventive medicine in America had resulted in a laissez faire attitude of many people toward their health. Indeed a concern with staying healthy frequently labeled one a "health nut." While recents trends in healthful foods and increased physical activity are to be applauded, the relative neglect organized medicine has shown to preventive medicine has resulted in the proliferation of individuals without sound training who profess to practice "holistic medicine." The casualties of this approach have already begun to be recorded. Cases of intoxication and death have been seen with people who were using "healthful herbs." An editorial in the *Journal of the American Medical Association* noted that this was probably just the tip of the iceberg. Popular magazines have been advocating the use of enormous doses of vitamin E and selenium in the prevention of cancer. However, a July 1977 issue of *Journal of the American Medical Association* carried an article that linked high selenium intake with amyotrophic lateral sclerosis. The use of laetrile for cancer prevention is another example of this dangerous trend.

Doctor Samuel Bosch of the Department of Community Medicine (CUNY) suggested a reason for this comparative lack of interest in teaching preventive medicine in medical school. With a medical system based almost exclusively on fee-for-service, interest in managing acute illnesses comes before methods of preventing them. He suggested expansion of prepaid medical plans that would be oriented more toward preventing illnesses. Meanwhile, federal funding of health care at all levels is bringing with it a concomitant interest in cost-effective programs and matériel. When health planners and medical practitioners must make choices about what new technological advance can or cannot be purchased, it appears that the time for developing new avenues to health care must be established. Development and utilization of very expensive equipment such as the computerized axial tomography (CAT) scanner has been criticized as not being cost effective because the number of individuals that can benefit is limited. On the other hand, considerable decreases in mortality and morbidity could be accomplished simply by physician's taking a more active role in intervention in the premorbid stages of disease.

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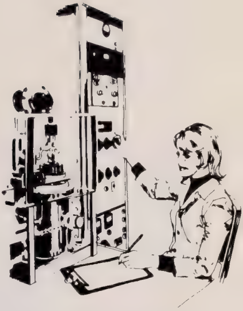

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Ralph Colp Award

The Ralph Colp Award for 1977/78 has been given to Drs. Michelle Nacchiero, Michael Adler, Piero Pieroni, and Tohru Takeshima for their papers "The Parotid and the Pancreas. I.: The Effects of Secretin, CCK-PZ, and Prostaglandin E_2 on Canine Parotid Secretion" and "The Parotid and the Pancreas. II.: Parotid Secretion in Canine Chronic Pancreatitis" (Volume 45, Number 2, March–April 1978 issue).

This award is made by the Ralph Colp Fund, for the best paper published in *The Mount Sinai Journal of Medicine* by a member of the house staff or a junior member of the attending staff. Preference is given to papers on surgical subjects. The Fund was established in honor of Dr. Ralph Colp, distinguished surgeon and long-time Chief of Surgery of The Mount Sinai Hospital.

The Globus Prize

In 1934 the late Joseph Globus wrote the opening editorial for the *Journal of The Mount Sinai Hospital,* (as it was then called), setting it in the path it followed until his death. It is the duty of each new Editor and the Editorial Board to reexamine the purposes of the Journal, and either to reaffirm the old aims or to fix new ones. We believe that a major aim of the Journal, now as then, is to make available its pages for case reports based upon the extraordinary clinical material which our Hospital has always had, some of which might otherwise be lost. Close observation, accurate, concise description, and detailed reporting are to be encouraged. We hope to foster the type of medical writing exemplified so brilliantly by men like Parkes Weber and Emanuel Libman. The Journal would prefer these papers to come from the ranks of the House and Resident Staffs, Fellows, and younger men in general, but all Mount Sinai Hospital doctors are encouraged to send in material. The subject may pertain to any clinical aspect of medicine surgery, or other specialty.

We therefore offer the 1977/78 Joseph H. Globus Memorial Prize for the best such paper published in the Journal to Janet Cuttner, M.D., for her paper "Chronic Thrombocytopenic Purpura: Report of a Case with Fine Relapses and Review of the Literature" (Volume 45, Number 3, May–June 1978 issue).

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THE MOUNT SINAI
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Malignant Melanoma in an Albino: Diagnosis Supported by Ultrastructure

LAURENCE I. ALPERT, M.D. AND IVAN DAMJANOV, M.D.

Abstract

A metastatic melanoma occurring in a young male albino, whose presumed primary skin lesion had been previously removed by fulguration, was confirmed on the basis of ultrastructural characteristics. These included the occasional presence of membrane-bound granular and fibrillar material often demonstrating concentric layering, structures interpreted as incompletely developed melanosomes. This case represents the eighth report of melanoma developing in an albino and the second studied by electron microscopy.

Despite the propensity for melanomas to occur with greater frequency in light-skinned persons, there have been but seven reported cases in the world literature of malignant melanomas associated with albinism (1-6). This may simply reflect the difficulty in establishing a definitive diagnosis without the use of special enzymatic histochemical or preferably ultrastructural methods to demonstrate the incompletely developed pigment granules characterizing the melanocytes of albinos.

We have had the opportunity to identify, with the aid of the electron microscope, a metastatic melanoma occurring in a young albino, the presumed primary skin lesion having been previously removed by fulguration without histologic sections. This is the second reported ultrastructural study of such a case.

Case Report

A 25-year-old albino Caucasian man was first admitted to Northern Westchester Hospital Center for evaluation of left inguinal swelling of 6 months' duration. Relevant history included the removal, 6 years previously, of a left knee skin lesion by electrodessication. No tissue had been submitted for histologic examination. Inguinal lymph node biopsy shortly after admission revealed metastatic carcinoma, whose histologic appearance was suggestive of an amelanotic melanoma (vide infra), presumably secondary to the previously fulgurated lesion of the knee. The patient was discharged without further treatment. He remained asymptomatic until 1 year later when he developed severe low back pain. Because of a consultant oncologist's reluctance to begin a course of immunotherapy for melanoma without a definitive diagnosis, he underwent exploratory laparotomy in order to obtain tissue for electron microscopy. He was found to have extensive retroperitoneal tumor, which was biopsied. Following discharge he was begun on a course of BCG immunotherapy, but has shown progressive clinical deterioration.

Light microscopic findings. The tumor consisted of nests of polygonal and occasionally spindled cells with well-demarcated eosinophilic cytoplasm, prominent nucleoli and frequent mitoses (Fig. 1). There was no evidence of pigment production by routine H&E staining or by special stains for melanin (Fontana-Masson).

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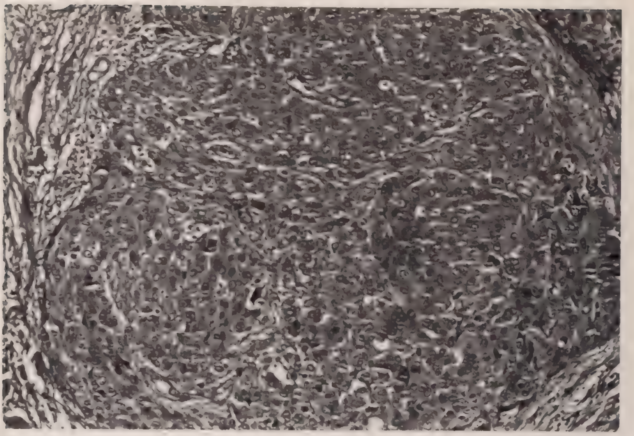

FIG. 1. Lymph node replaced by nests of polygonal cells showing deeply eosinophilic cytoplasm, prominent nucleoli and numerous mitoses. Pigment is not demonstrable (H&E, × 100).

Ultrastructural studies. Tissue was fixed in glutaraldehyde, post-fixed in osmium tetroxide, stained with uranyl acetate and lead citrate and examined using a Philips 300 electron microscope.

The tumor cells showed abundant cytoplasm containing numerous spherical mitochondria, and a well-developed rough and smooth endoplasmic reticulum. Many cells had prominent Golgi apparatuses. Some cells contained large membrane-bound granules composed of fine granular and fibrillar material (Fig. 2 a,b,c). In addition there were fibrillar and granular aggregates, which were partially membrane bound.

Discussion

Using a technique of gold impregnation of skin sections Becker in 1952 (7) demonstrated that epidermal melanocytes were present in normal numbers in individuals with oculocutaneous albinism. It is generally accepted today that the pigmentary abnormality in this condition may result from a deficiency either of tyrosinase or, less frequently, of its substrate tyrosine, each controlled by a separate gene locus (8). In either case the result is the inability to form fully pigmented granules from preexisting melanosomes. Consequently the dopa and tyrosinase reactions are negative in the preponderant group.

While the vulnerability of the adult human albino skin to actinic-induced squamous and basal cell carcinomas is well recognized, especially among albino blacks living in the tropics (4), the incidence of melanoma is exceedingly rare.

FIG. 2. a) Numerous irregularly shaped melanosomes in the perinuclear cytoplasm × 16.000; b) Lightly pigmented membrane-bound melanosome (arrow) has a fibrillar internal structure. Partially membrane-bound granular material (arrowheads) representing most likely abortive melanogenesis × 29.000; c) Membrane-bound melanosomes having fibrillar internal structure, often with concentric layering (arrow) × 32.000.

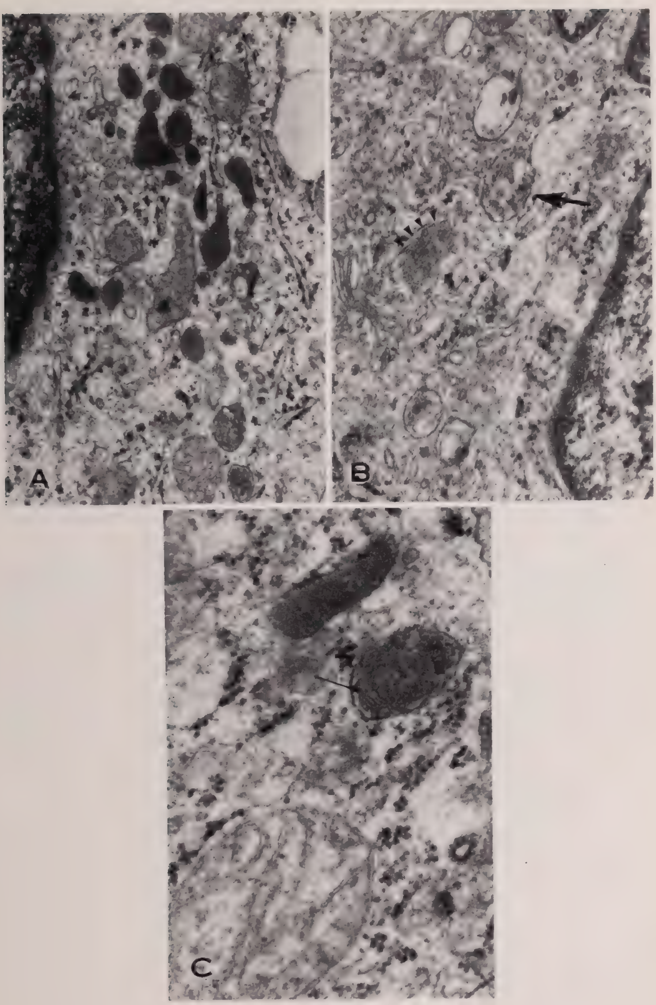

FIG. 2 A-C

Of interest are several clinical findings in the seven reported cases, including the present subject: six were males, all were relatively young, and four of the seven melanomas appeared to have arisen from long-standing pre existing nevi.

Klug and Günther (9) studying ultrastructural differences among a large series of human melanomas distinguished two different tumor forms. The first (Type A) was composed of cells that contained cigar-shaped mature melanosomes and premelanosomes having an internal helical structure exhibiting periodicity. Tumor cells of the other basic form (Type B) contained only spherical melanosomes and premelanosomes showing no internal fibrillar structure. These melanosomes could not be differentiated from lysosomes by ultrastructure. The appearance of melanosomes in our case were intermediate between these two types, having an oblong configuration with occasional ones demonstrating a concentrically layered fibrillar structure. Melanosomes were never heavily pigmented and the typical periodicity of Type A melanosomes was not observed.

From the experience of this and the six previous cases of melanomas occurring in albinos, it would seem wise to remove all nevi at an early age, making sure to obtain histologic verification. The occasional application of the electron microscope to the identification of tumors lacking conventional histochemical reactions is also evidenced by this case.

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Goodpasture's Syndrome with No Overt Renal Disease

PRATAP SARAF, M.D., HERBERT W. BERGER, M.D., AND SWAN N. THUNG, M.D.

Abstract

We report a 25-year-old man with repeated hemoptysis, diffuse pulmonary infiltrations, and anemia, but with no hematuria or proteinuria. The diagnosis of Goodpasture's syndrome was established from characteristic immunofluorescent changes seen on both kidney and lung biopsies. Corticosteroid therapy was followed by an abrupt and sustained resolution of hemoptysis. Over a follow-up period of 20 months no further episodes of hemoptysis occurred and no renal abnormalities developed.

Usually Goodpasture's syndrome presents with hemoptysis, pulmonary infiltrations, anemia, hematuria, and proteinuria which are followed in a variable period of time by progressive renal failure (1, 2). Corticosteroid therapy may be efficacious before renal failure appears (1, 2). Immunosuppressive agents have not been found to be superior to steroids (2). Intermittent peritoneal dialysis, hemodialysis, bilateral nephrectomy followed by renal transplantation, and plasmapheresis combined with immunosuppressive therapy have been employed in individual cases (3, 4).

Mathew and colleagues (5) described successful corticosteroid treatment of a patient with hemotypsis who had no hematuria or proteinuria. We report a similar case in which Goodpasture's syndrome was manifested by recurrent hemoptysis and pulmonary infiltrations and the diagnosis was established by immunofluorescent studies of lung and kidney biopsies. Following treatment with corticosteroids pulmonary hemorrhage terminated abruptly. The patient did not develop renal abnormalities in the ensuing 20 months. This case illustrates that the diagnosis of Goodpasture's syndrome can be established in the absence of hematuria and proteinuria by immunofluorescent studies of kidney and lung biopsies and that early treatment with large doses of corticosteroids may alter the usual natural course of the disease.

Case Report

A 25-year-old man from the Dominican Republic was admitted to the Mount Sinai Services-City Hospital Center at Elmhurst on July 19, 1975, with hemoptysis for three days. There was no history of fever, night sweats, or weight loss. He had been employed in a poultry market where he skinned chickens. On admission the patient was in no distress. His blood pressure was 110/70 mm Hg. Physical examination was normal. X-ray films of the chest showed diffuse consolidation of both lungs, most prominent at the bases. The hemoglobin level was 14.1 g/dl, the white blood cell count 12,600/mm^3 with 18% eosinophils. The arterial oxygen pressure (PaO$_2$) was 82 mm Hg on

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room air. There was no proteinuria or hematuria. A fiberoptic bronchoscopy performed after hemoptysis stopped did not reveal the source of bleeding. Under light microscopy a transbronchial lung biopsy showed hemosiderin-laden macrophages with a small number of eosinophils. Several sputa for acid-fast bacilli and fungi were negative. An intermediate-strength tuberculin skin test showed 15 mm induration after 48 hours. The chest x-ray cleared in three days.

Two weeks after discharge hemoptysis recurred and increased in amount and frequency until the second admission on August 28, 1975. At this time the patient was in moderately severe respiratory distress. Bilateral rales were heard. A chest x-ray again showed extensive bilateral alveolar infiltrates. The arterial oxygen pressure (PaO_2) was 48 mm Hg on room air. Hemoglobin level was 10.6 g/dl, white blood cell count 11,100/mm^3 with no increase in eosinophils. Fiberoptic bronchoscopy showed active bleeding from both the right and left bronchial trees. Again there was no hematuria or proteinuria. An intravenous pyelogram was normal. Blood for antiglomerular basement membrane antibodies was negative. Complete coagulation studies and tests for antinuclear antibodies, rheumatoid factor, and cold agglutinins were negative. Hemoptysis ceased within three days and the chest x-ray showed rapid clearing of the infiltrates. Renal biopsy appeared normal under light and electron microscopy. However, immunofluorescent staining of sections showed linear deposits of IgG and fibrinogen and focally linear deposits of complement (β_1C) along the capillary walls (Fig. 1). Stains done on the lung sections obtained from the previous admission showed similar deposits along the alveolar walls except for the absence of fibrinogen. The patient

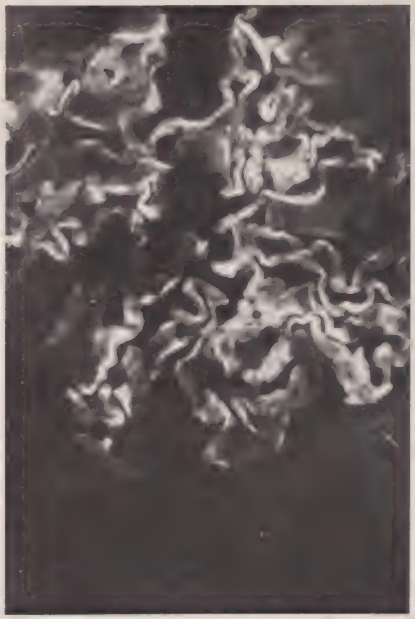

FIG. 1. Immunofluorescent stain of renal biopsy specimen showing linear deposits of IgG along glomerular capillary walls.

was started on prednisone 30 mg per day and isoniazid 300 mg per day on October 8, 1975. There were no further episodes of hemoptysis. The patient was followed in the Chest Clinic for over 20 months without reappearance of hemoptysis, anemia, or development of hematuria or proteinuria. A repeat renal biopsy with immunofluorescent studies done in January 1977 showed changes similar to those in the previous biopsy except that fibrinogen was not present.

Discussion

The usual criteria for establishing a diagnosis of Goodpasture's syndrome include 1) a history of recurrent hemoptysis with rapidly clearing pulmonary infiltrates, 2) microcytic hypochromic anemia, 3) glomerulonephritis manifested by hematuria and proteinuria, 4) positive immunofluorescent studies showing linear deposition of IgG along the glomerular and alveolar basement membranes, and 5) antiglomerular basement membrane antibodies in the serum. With few exceptions, the natural history of Goodpasture's syndrome includes recurrent pulmonary hemorrhage and progressive renal failure (1, 2). Corticosteroid therapy has generally not been successful after the onset of renal failure (1, 2).

Mathew and colleagues (5) reported a patient with several bouts of hemoptysis but no hematuria, proteinuria, or elevation of blood urea nitrogen. Renal biopsy showed minimal changes on light microscopy, but immunofluorescent studies showed linear deposits of IgG, IgM, IgE, IgA, fibrinogen, and complement along the capillary basement membrane. No mention was made of serum antiglomerular basement membrane antibodies and a lung biopsy was not performed. The patient was treated with 60 mg per day of prednisolone after the second episode of hemoptysis and remained asymptomatic for 15 months subsequently.

Our patient had recurrent hemoptysis, pulmonary infiltrates, and anemia, but no hematuria or proteinuria, and is similar to Mathew's except that he had lung sections showing linear deposits of IgG and complement in addition to positive immunofluorescent studies of the kidney. The patient was started on prednisone 30 mg per day because of life-threatening pulmonary hemorrhage, based on the premise that therapy might prevent the progressive renal dysfunction which occurs in Goodpasture's syndrome. The abrupt and sustained resolution of symptoms shortly after institution of corticosteroids mandated continuation of this therapy. The significance of the persistent immunofluorescent abnormalities found on the repeat renal biopsy is not clear, but as noted by Teichman (6), may represent residual adherent immunoglobulin bound during the period of active disease.

This patient could have a form of idiopathic pulmonary hemosiderosis (IPH). However, in IPH there is a different age distribution and lung biopsy shows focal ruptures of basement membrane and hydropic changes in pneumocytes which were absent in our case (7, 8). In addition, the presence of immunofluorescent deposits on both the renal and lung sections is in favor of Goodpasture's syndrome, not IPH (8, 9).

When patients present with repeated hemoptysis and a radiologic picture compatible with Goodpasture's syndrome but no hematuria or proteinuria, a definitive diagnosis should be sought either from a lung or kidney biopsy. Since light and electron microscopy may not be diagnostic or may even be normal, immunofluorescent studies must be done to demonstrate the typical pattern seen in Goodpasture's syndrome. Patients with early Goodpasture's syndrome should be started on corticosteroid therapy, particularly in the absence of hematuria and proteinuria, as this may help avert the renal deterioration seen in this disease. The proper duration of therapy is still unknown and will require long-term follow-up of patients such as presented in this report.

Acknowledgment

The immunofluorescent studies were interpreted by Dr. Michael Gerber, Department of Pathology, Mount Sinai School of Medicine.

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Gigantic Bilateral Aberrant Axillary Breasts: A Case Report

VIRATANA CHAROENKUL, M.D. AND PRASARN JIMARKON, M.D.

The mammary ridge or milk line is developed from an ectodermal thickening extending from the axilla to the groin. It can be seen first at the sixth week in the human embryo. The pectoral thickening progresses with the ultimate formation of the breast. This pectoral location of the breast in humans is similar to other mammals, e.g., elephants and sea cows, but in contrast to the multiple breasts of dogs and pigs and to the inguinal location in cows, goats and whales.

Developmental disorders of the breast in humans resulting in additional breasts in the milk line occur in about 1–6% of the population (1, 2, 3). It is approximately twice as common in females as in males (4). Supernumerary nipples and breasts are observed less frequently in Caucasians than in Orientals (5). They are commonly mistaken for moles. They may not become apparent until the breast tissue is stimulated by pregnancy and lactation. Most of these aberrant axillary breasts are small in size. We found no reports in the world literature of large aberrant axillary breasts in the 1,500 gm range, as noted in this case report. We believe the following case presents a patient with the largest recorded bilateral axillary breasts noted to date.

Case Report

A 37-year-old Thai woman farmer, para 9–1–1–7, complained of masses in both axillae in the past four years. She first noticed the thumb-sized lumps in both axillae after giving birth to her sixth child. Since the amount of milk secreted for breast feeding was inadequate, she took some herbs for stimulation of milk production. Two days after taking the medication, milk production became adequate. Also, she noticed milk being produced from the lumps in both axillae for two to three days. This child died at age of one month of uncertain causes. Two months later, she became pregnant with her seventh child. During pregnancy she noticed the axillary lumps had enlarged to lemon size. After delivery, she took the same herbs for milk stimulation and breast fed her child for one and a half years. On her eighth pregnancy both the axillary masses were enlarged to about the size of a grapefruit. Again, she took the same herbs for milk stimulation, however, she was only able to give breast feeding for six months owing to difficulty in feeding. In early 1977, during the fourth month of her ninth pregnancy, she noticed that these two axillary masses had rapidly enlarged. She felt the heaviness of the lumps which had became painful and had difficulty in breathing. She lost weight and had spells of fainting on many occasions. On the tenth day of puerperium she came to the "K" hospital in Bangkok, Thailand. On admission she was anemic (Hg 9 gm%). Both of her breasts were engorged and pendulous, extending down to her waist (Fig. 1). The two axillary masses were also engorged, had nodular surfaces and were tender. At the tips of *both axillary masses* there were areas of hyperpigmentation, more pronounced on the right,

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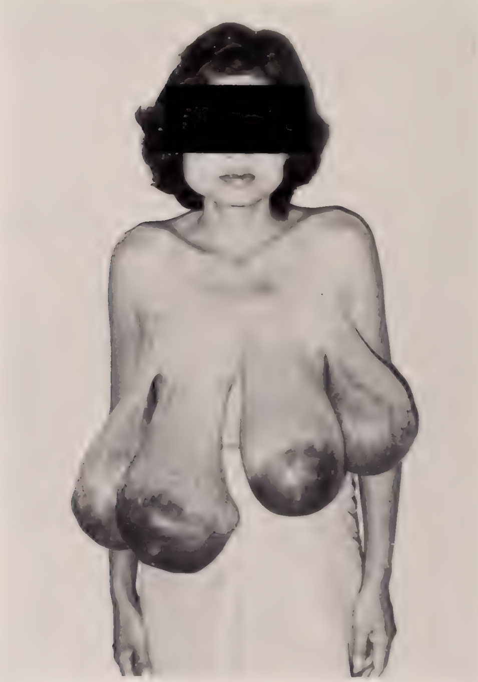

FIG. 1. Bilateral aberrant axillary breasts and hypertrophy of breasts.

representing the areolae. There were no nipples and no secretion could be extruded from these hyperpigmented areas. Mammography was performed. No calcifications were seen. Due to pain and heaviness, the axillary masses were removed. The left mass weighed 1500 gms and measured 13 × 10 × 8 centimeters. Sections showed multiple large cysts containing milk-like fluid. The rest of the tissue was yellowish white in color with lobulated surface. The right mass weighed 1490 gm. It measured 14 × 10 × 6 centimeters. Sectioning revealed features similar to those in the left mass (Fig. 2). Microscopic examination revealed dilatation of excretory ducts with galactocele formation, hypertrophy and hyperplasia of mammary glands (Fig. 3).

Discussion

Aberrant axillary breasts have been observed to be hereditary since 1837 (6). However, no hereditary trait can be traced in this case. In a review of literature we cannot find any other reports of large aberrant axillary breasts of dimensions similar to this case. The aberrant breasts reported in this case enlarged during pregnancy. This has also been found in most reported cases.

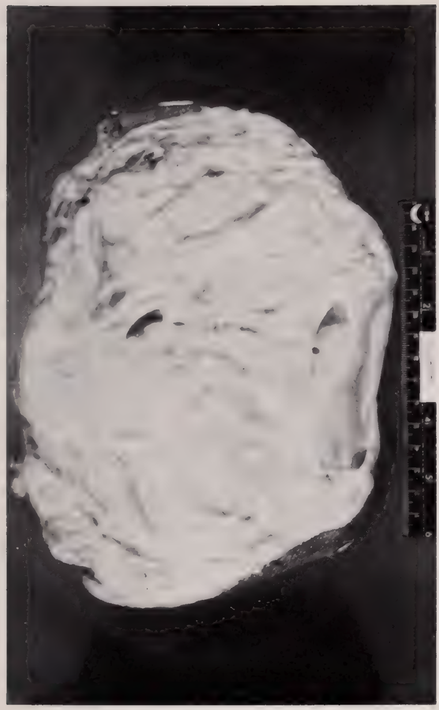

FIG. 2. Cross-section of the right aberrant axillary breast showed multiple cysts containing milk, and lobulated surface.

The presence of all breast elements is not necessary for diagnosis. Aberrant breast has been classified into eight categories (7) according to the structures present:

1. Complete breast: mammary gland tissue, nipple and areola.
2. Glandular tissue and nipple.
3. Glandular tissue and areola.
4. Glandular tissue only.
5. Nipple and areola with an area of fat replacing mammary glandular tissue-pseudomamma.
6. Nipple only—polythelia.
7. Areola only—polythelia areolaris.
8. Patch of hair only—polythelia pilosa.

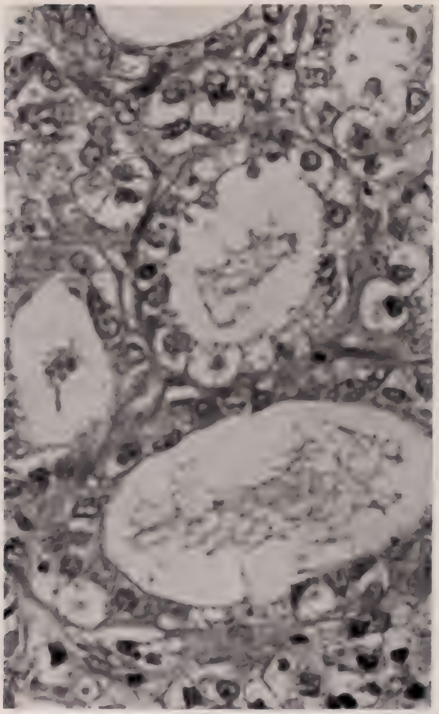

FIG 3. Mammary acini lined by low cuboidal epithelium. The cells have uniform nuclei. The cytoplasm is vesicular. Acidophilic material is noted in the lumen. H&E stain, high power ×500.

This case did not give a history of noticeable masses or evidence of aberrant breast since childhood. The patient did not notice the masses until her sixth pregnancy. Similar findings have been noted in many other cases reported (3). The herbs which the patient had taken during her lactation periods are still being studied for their possible role in stimulation of breast enlargement.

Conclusion

In previous studies, axillary breasts have been found to be hereditary. There is no such history in the present case. Some genetic disturbances could result in a variable failure of regression of the mammary ridge, as in this case. These axillary breasts enlarged and became apparent during pregnancy and the lactation period. Their large size was quite striking and they are believed to be the largest axillary breasts that have been reported.

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Judging the the Degree of Suicide Risk through the Clinical Interview

STANLEY FRIEDMAN, PH.D., M.D., PAUL FRIEDMAN, PH.D., M.D., AND HELGA JUSTMAN, M.S.W.

Abstract

The field of medicine contains many clinical situations in which the physician is called upon to make decisions of a life or death nature. Judging the severity of suicide risk is one of them. Further, this judgment cannot be supported by objective signs and the data may be markedly distorted by the patient's need to conceal suicidal intentions, a situation without parallel in any other sphere of medicine. Some indicators of suicide risk, potentially observable during the clinical interview, are reviewed. These include sex, age, previous suicide attempts, history of past and current object loss, the presence of symptoms relating to death, lack of plans for the future, magical meanings of death, and sudden and unexplained alleviation of symptoms of depression.

Introduction

Over 20,000 people in the United States kill themselves every year, thus ranking suicide as the eleventh leading cause of adult American deaths (1). The actual rate is much higher since many deaths due to suicide are not so recorded because of religious, social, and moral reasons. Many incidents of sudden death due to ingestion of poisons and medications or due to inhalation of gases are listed as accidental, when, in reality, they are intentional (2). If one takes into consideration the slow suicide of chronic alcoholics or camouflaged suicides through automobile collisions or "accidental" overdosing with tranquilizers, the statistics might amount to as many as 100,000 deaths a year. All these factors highlight the importance and extent of the problem of suicide.

Because of its danger to the patient, potential suicide represents one of the most difficult situations for psychiatric appraisal (3, 4). In addition, the seriously suicidal patient is not only not motivated to be truthful during the psychiatric interview, but indeed, is actually quite likely to conceal a determination to kill himself. This clinical difficulty also applies to the recent use of the questionnaire-type self-rating tests of depression and suicide potential (5, 6, 7). Therefore, the accurate judging of the degree of suicide risk by the psychiatric interviewer is of the utmost importance. The purpose of this report is to attempt to review certain clinical factors that can be used by the clinician as a reflection of the seriousness of suicidal intentions.

Research Sample

The data used in this report are from a series of 82 patients who were admitted to the Inpatient Service of the Institute of Psychiatry of The Mount

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Sinai Hospital after having attempted suicide. Each patient was seen as soon as possible after admission and evaluated by a lengthy clinical interview that included responses to a detailed questionnaire of 151 items. The questionnaire covered areas crucial to the patient's past history and included questions about family structure, object relations and loss, psychosexual development, and character of parents. In addition, one of the two senior authors supervised the psychotherapy of a limited number of our subjects in order to obtain data from potentially deeper layers of the personality.

The sample was also divided into a dichotomy based on whether or not a serious suicide attempt had been made in order to see if seriousness of attempt correlated with any variables studied. This classification had as its criterion the possibility that the patient could have died without intervention and medical attention. The reliability of inter-rater judgment for this dichotomy was significant at below the .01 level of confidence (agreement in 77 of 82 cases).

Specimen Case (Case 1)

This case is used as a specimen case for a number of reasons. First, her history reflects a number of factors that will be reviewed in the course of this paper. Second, patient's high intelligence and the weakness of her defenses allow for the obtaining of richer than average data. Finally, the patient's relative affluence and her freedom from limiting environmental factors such as race or religion allow us to exclude various environmentally based frustrations as contributing factors to her suicidal impulses.

Mrs. X is an attractive 25-year-old married suburban housewife. Seemingly poised and good humored, she is highly verbal and can describe her emotional difficulties with a rich vocabulary and more than a trace of ironic humor.

The patient describes a series of recent events that have led to three suicide attempts of increasing gravity over the preceding year. The birth of her only child about two years ago created an endopsychic environment in which suicide was possible. Although she had felt very well during her pregnancy, she "fell apart" following childbirth. A nurse had been hired to live in and help with the baby. Although this created an objectively easy situation, the patient felt clumsy when she handled the baby, incompetent as a mother, and soon was too anxious when with him to pick him up since she was afraid that she would drop and injure him. Her anxiety and depression reached its first nadir when he was about one year old. At this time, he fell and hurt himself and went to the nurse, calling "Mamma." The patient felt that this confirmed her worthlessness as a mother. At this time, she began her earliest suicide gestures, although they were not severe ones. She would take a sleeping pill, wake up after an interval and take another, and continue to do this. However, it did not escape her attention that there was a built-in safety factor of remaining asleep beyond a certain dosage level.

The patient began to feel increasingly isolated in her own home as her child and the nurse closely interacted. Her second suicide gesture occurred when the child was $1\frac{1}{2}$ years old. He came looking for her while she was bathing. The nurse told him that the patient was out shopping and the two of them departed. Again, the patient felt depressed and incapable of being a mother. Impulsively, she took five Valium pills, became frightened, and called her husband.

The most recent and very serious suicide attempt was related to the fact that a friend had gone to her (the patient's) obstetrician and had recently given birth. The patient described her profound envy of this friend because she had developed "a big crush" on the obstetrician during her own pregnancy. She had thought that she had "gotten over this crush" but her envy made her realize that she was wrong. "SHE [her friend] felt wonderful; SHE had natural childbirth; SHE was doing everything just right; and I was miserable." She described her feeling that her friend was so much more womanly, healthy, attractive and maternal in this doctor's eyes than she could ever be. After visiting this woman, the patient became profoundly depressed, feeling that her psychiatrist and her husband would find intolerable her "whining again about the same old thing." Sure that both despised her and could not understand how she felt, she decided that she "would show them." She took 16 Doridens early in the morning, intending to return to sleep and die, but became frightened and told her husband. She was hospitalized in the Intensive Care Unit where she remained in coma for $2\frac{1}{2}$ days.

The patient's description of her early life sounds like an almost exact prototype of her last two years. The most crucial factors in this early development were the birth of a sister when she was two years old and the death of her father when she was $2\frac{1}{2}$ years old. With the birth of her sister, a nurse was hired to take care of the two children. The patient, however, describes her sister as being so sickly as a baby that the nurse spent all of her time holding and taking care of her. "You know, she did not like me. I would just hear her say, 'Shut up. I'm busy with the baby.' This is the first time I can realize that all this is somehow connected with my sister." The patient's description makes it clear that the current situation with her baby and the nurse is a recreation of the past where she felt rejected by the nurse's attention to her rival sister.

The patient does not recall the death of her father. She then adds that her mother told her that she (the patient) did not seem to care. The mother remarried when the patient was four years old. She decribes a household in which everybody had a love object except herself. Apparently, her stepfather wanted nothing to do with the children. Because of this, he took her mother to a separate floor of the building. "They lived on one floor and we girls and the nurse lived on another, but the nurse was only with my sister so I was alone." In addition to the reproduction of her early sibling rivalry, the friend who gave birth seems to represent a condensation of the favored, more valuable sister and, at the same time, the mother who found it easy to get another man to love her.

The patient presents other data which are not so readily understood but which are extremely provocative. For example, her stepfather, the man who rejected her, committed suicide shortly before the patient's first suicide gesture. In addition, the patient's serious suicide attempt occurred when she was 25 years old, the same age as her father when he died. Finally, it also must be noted that some of her pathology may relate to an identification with her sister who has severe psychiatric problems and who is currently awaiting a divorce.

Review of Pertinent Clinical Factors in Judging Suicide Risk

There are various signs of suicide risk that are sufficiently familàr that they will be mentioned but not stressed in this report. In proportion to their importance, such factors as severe depression (8, 9) and the truism that added danger accompanies its gradual improvement are well-known examples. The lack of stress on these factors is only related to our understanding that they are sufficiently familiar to clinicians. Instead, we will stress certain factors in the clinical situation that are less obvious and familiar but which may provide additional help in uncovering suicide intentions. The potential importance of such clinical factors can be seen by the following factors in our sample. The first is that 41 of the patients were seeing psychiatrists (N = 16) or other physicians (N = 25) at the time of the suicide attempt but the impending act was insufficiently appreciated. In addition, none of the patients had ever contacted any suicide prevention center, and only three had gone to a hospital emergency room shortly before the suicidal act or gesture.

As with all clinical situations, the factors of probability and judgment play important roles. We can recognize that this is not on the highest level of scientific inference, but we can also be aware that such clinical judgments may be the only ones available to us when we are called upon to appraise the risk of suicide (10, 11). In addition, these judgments must be based upon factors of differing empirical value. For example, these will include low-level judgments based upon statistics (12), on the application of logic, and on empiric generalizations with small samples. The following headings comprise those factors that have seemed additionally useful in gauging the suicide potential of a patient through the clinical interview. They include sex, age, history of previous suicide attempt, history of object loss, neurotic symptoms relating to death, lack of plans for the future, indifference to or magical attitudes towards death, and sudden alleviation of a depression.

A. *Sex*

It is well known and frequently reported that suicide attempts are approximately four times as common among females and that successful suicide is approximately four times as common among males (12, 13, 14, 15). All other factors being equal, it is clear that the male represents the greater threat of self-destruction. These data are supported by the present sample. Comparing serious attempts with gestures, 46% of the serious attempts were carried out by males. In contrast, only 11% of the gestures were carried out by males. This difference is significant at the .001 level of confidence (t = 4.67).

B. *Age*

Statistical reviews note that there are ages of higher suicide potential and these sensitive ages must be part of the appraisal within the clinical situation (12, 13, 15). The ages most often indicated in the literature are late adolescence, early adulthood, and the late sixties. Our series of suicide attempters were compared to a sequentially selected series of psychiatric admissions to The Mount Sinai Hospital who had no history of attempted suicide. This was done in order to compare our sample with a psychiatric instead of a normal population. Our findings were in agreement with the literature in only one category. There was significantly greater proportion of suicidal patients between the ages of 16 through 30 (62% to 45%, $t = 2.50$, significant at the .02 level of confidence). The specimen case, above, fulfills these criteria for age and sex.

C. *History of Previous Suicide Attempt*

The presence of a previous suicide attempt is extremely important in judging the degree of suicide risk. It indicates that not only has there been a conscious impulse to destroy oneself; it also indicates that control over such self-destructive impulses is so weak that the patient has come close to killing himself in the past. In our current sample of 82 patients, the suicide attempts of 37 of them could be described as serious and that there was a strong possibility that the patients could have died. Of these 37 patients, 16 had a history of a previous serious suicide attempt. It is occasionally claimed that the presence of mild suicide gestures implies less likelihood of a serious suicide risk. However, in the current sample, 19 of the 37 patients who made serious attempts had a history of a previous mild gesture. These gestures included small doses of tranquilizers or aspirin, and the infliction of superficial wrist cuttings. It is noteworthy that the specimen case had two previous types of suicide gesture but that these were followed by a serious attempt that led to a $2\frac{1}{2}$ day coma.

If the group making a serious suicide attempt is compared to the group making a mild attempt or gesture, the serious group has a statistically significant greater number of previous attempts. However, this difference is an artifact since the serious attempt group was older. In addition, as noted above, over half of the serious attempt group had made at least one previous mild attempt or gesture, implying that at least some patients begin with gestures but end with a serious attempt.

D. *History of Object Loss*

The most important statement of the etiology of suicide was made by Freud in 1917 (16). Here, Freud not only stressed the unconscious murderous impulse towards an object, but also the importance of an identification with this object when it is lost. Clinically, we should expect to find evidence of such object loss, both recent and remote, and such findings should increase our concern with the suicidal potential of the patient (17, 18). In the current sample, 24 of the 37 patients who made serious suicide attempts had suffered a recent object loss. Seventeen were aware of some object loss occurring before the age of 15. In addition, 12 were consciously aware of a recent threat of object loss. Of the 37 subjects, 31 had been involved with some form of consciously known object loss. However, no significant difference was found when this group was compared to the group with mild attempts or gestures, the latter group reporting only slightly lower figures.

Case 2

A 65-year-old woman lost her favorite child after a brief and unexpected illness. She made a serious but unsuccessful suicide attempt shortly after this tragedy. After recovering from the physical effects of her attempt, she claimed to be improved psychiatrically. However, as soon as she was left unguarded, she made a second and successful attempt with the sleeping pills she had gradually accumulated since her first attempt.

Case 3

This type of case is common in our sample (N = 8) and can be described as a group. Typically, an adolescent girl or young woman makes a mild, impulsive suicide attempt or gesture following rejection by a sweetheart. However, investigation reveals that her remote past contains much object loss. Most frequently, this history is of a father who deserted or was away from the home much of the time.

Case 4

Overt object loss is not essential since the inner feelings of loss may relate to events, such as the birth of a sibling, divorce, etc., in which the child feels abandoned. A disturbed young woman would occasionally announce an impending marriage engagement to her father. The man would always seem an inappropriate choice to the father and he would vigorously object. Puzzled by his daughter's announcements, he consulted a physician friend and was advised to call his daughter's bluff by approving of her next choice. He did so and the daughter made a prompt suicide gesture.

E. *Neurotic Symptoms Relating to Death*

Since potential suicides have a hypercathexis of thoughts and wishes relating to death, we should not be surprised that these thoughts, especially if still unconscious, will achieve motility through some symptoms related to death. Severe hypochondriasis, death obsessions and phobias, such as cancerphobias, are examples of such symptoms (N = 11).

Case 5

An analytic patient began her treatment with a symptom of a fear of falling to her death (19). After about a year in treatment, this symptom was succeeded by the idea of jumping. Later yet, a conscious wish to jump emerged and the patient was then aware of her chronic suicidal wish. Interestingly, she simultaneously became aware of her previously unconscious patricidal and fratricidal impulses.

Case 6

A hospitalized patient had made a serious suicide attempt after her husband had left her with the parting comment that she was crazy and that he would get custody of their three sons. Fortunately, she was found by a neighbor and taken in coma to the hospital. Interviews revealed a series of obsessional fears that her children would die. "I look at them when they sleep because I am afraid they will die. I watch them when they play in the house because boys are wild and they might accidentally jump out of the window. Other mothers let their boys go to school alone, but I take mine there because they might get run over." It is also of interest that the patient had led a somewhat satisfactory life with her husband until her first pregnancy. She was married, held a job, and had a satisfying sex life. With pregnancy, however, she developed severe insomnia and marked G.I. tract hypochondriasis, and made a mild suicide attempt in the sixth month of pregnancy. Following delivery, she became sexually frigid and developed her obsessional symptoms about death.

It is reasonable to assume that symptoms relating to death become more ominous if they are of recent appearance, if they become more intense, or if they change their form. However, we can see that even with an unchanging symptom pattern (Case 6), an external trauma, such as desertion by a husband, can destroy a precarious balance.

F. *Lack of Plans for the Future*

The patient who plans to kill himself is also frequently determined to hide this fact from the examiner. Much attention has been paid to the covert appeals for help and rescue that frequently accompany suicide attempts (12). It may be that this stress on such appeals impairs our awareness of that other side of the ambivalence that produces concealment of suicidal motives. Because of this, any clinical interviewing techniques that expose secret suicide intentions are important to mention. With our sample, it could be seen that patients with serious suicidal intentions had no long-range plans for other activities. If the interviewer makes a point of learning of the pre-suicide attempt interests and activities of the patient, the presence or absence of plans for the future may help in gauging the degree of suicide threat.

Case 7

A patient had made a serious suicide attempt that had led to coma and his psychiatric admission. The patient was pressing for discharge after a moderately long hospitalization. His Resident Psychiatrist and the Chief Attending on the ward felt that he still presented a serious suicide threat and asked for the opinion of one of the writers. Just prior to admission, he had been actively seeking a new job, had been in psychotherapy, was consistently transvestite in dress, and had been receiving sex hormone treatment. During the consultation, however, questions relating to his future plans in all these crucial areas were met with vague answers or absence of any plans. Because of this lack of interest in or planning for the future, the consultant agreed with the others' appraisal and the patient was referred for long-term hospitalization. Unfortunately, he was discharged from this other hospital after a few months and killed himself shortly thereafter.

G. *Atypical Attitudes toward Death*

The actively suicidal patient is in a state of marked endopsychic crisis. Even at times when the most intense suicide threat has lessened, many manifestations of regressed ego functioning are still detectable. Since the prospective suicidal patient has conscious thoughts about dying, we can expect that the idea of death has been regressively influenced by magical thinking of various sorts. The most familiar way that suicidal patients deal with the concept of death is to make it seem inconsequential, similar to life, or an improvement on it (N = 82). Another distorted idea of the meaning of death is that death itself is denied through magical ideas of immortality, and patients can occasionally tell of such ideas (N = 14).

Case 8

A patient who made a serious suicide attempt believed that human life is only one of many manifestations of energy. Therefore, all people are immortal even though their lives might be expressed in different forms. "I might be a star or comet careening through the heavens. I might not even have a physical form, but I think all people maintain their intellect after death."

Case 9

This patient made a mild suicide attempt consisting of an overdose of tranquilizers. She spontaneously described her belief in reincarnation and her reassurance that, if she had died, she would have returned in another animate form. "I'd like to be a bird, a beautiful bird to be admired."

H. *Sudden Alleviation of Symptoms of Depression*

A common clinical truism regarding the risk of suicide is that gradual improvement of a depression can indicate such a serious threat. It is thought that the intensely depressed patient cannot muster sufficient energy and decisiveness to kill himself. With improvement, however, the degree of depression may still be sufficient to harbor a suicidal wish while the increase in activity level now makes it possible to commit the act. Less attention is paid, however, to the fact that a *sudden* lifting of the depression can also be related to an increased suicide threat. A small number of patients in this sample (N = 3), all of whom made serious attempts at suicide, could readily recall that the decision to kill themselves led to a prompt remission of severe depressive symptoms. Typically, these patients concealed their suicide intentions. Thus, the only clinical manifestation of suicide risk was the sudden and unexplained improvement in the depression.

Case 10

A patient was severely depressed and felt beset by overwhelming external problems. "I suddenly realized that killing myself would solve everything. As soon as I decided to commit suicide, I wasn't depressed anymore. I had my solution and there wasn't anything to be sad about."

Judging Severity of Future Suicide Risk Following a Suicide Attempt

The suicidal patient presents a chronic risk in the future. Except for a rare handful of situations, a patient who has made a suicide attempt may make another more successful one in the face of future disruptions of his psychic economy, whether externally or internally provoked. Because of this, the clinician is always put into situations in which he must make judgments of future risk and he must balance the various factors known to him in reaching a decision concerning patient management. It is obvious that the clinician's effectiveness in such decision-making will be based on his knowledge of the various indicators of suicide risk and of his understanding of the psychodynamics of the patient. Each patient will have his own idiosyncratic background for suicide crisis, and proper management of the patient must include awareness of the genetic and dynamic factors that are crucial to each patient. Because our knowledge of the patient's conflict situation will always be incomplete, our ability to gauge degree of risk will be very imperfect; yet, such clinical evaluations will be the only basis for decisions that may block suicide attempts without recourse to frequent hospitalization. This type of clinical prediction will be exemplified, below, using the Specimen Case as an illustration.

Within the confines of our temporally limited and relatively meager knowledge of this woman, a number of factors are apparent. It seems that an endopsychic environment that made suicide a possibility began with the birth of her only child. In addition, the two suicidal gestures occurred in situations where the baby and his nurse were together and where the patient felt inadequate as a mother. This impression is markedly reinforced when the patient's early childhood can be reviewed in this context. The observer is left with the strong impression that the patient was reliving a situation of sibling rivalry in which she felt herself to be deserted by her mother and the nurse who took care of her sister and herself. More speculatively, it is possible to think that the birth of her own child revived a genetically old wish to destroy her baby sister and that the current derivative of this archaic wish was an infanticidal impulse, ultimately turned against the self in the suicidal act. When this conclusion is reached, the next step in the management of this patient would be to discourage any further childbearing. At first glance, this might seem to be a severe sacrifice for the patient but she will most likely be secretly grateful for the prohibition since her severe conflicts leave her with strong infantile wishes to be taken care of. Without further pregnancies, it can be hoped that the development of her child will lead her situation away from its resemblance to her own early childhood and thereby diminish the threat of suicide. In addition, however, an awareness should be maintained that the patient has current contact with her sister and that any severe difficulties or great successes that this sister encounters will have their reverberations within the patient's psychic structure.

Management of this patient must also include an awareness of her sensitivity to object loss. She made her first suicide gesture shortly after the suicide of the stepfather and her serious attempt when she was the same age as her father when he died. Situations related to these events must be regarded as suicide provocations. Possibilities of this would be far ranging, from being left by her husband to reaching her stepfather's age when he died.

The discussion, above, has stressed certain environmentally based possibilities that would revive the patient's infantile conflicts. In addition, changes in her internal environment may have a similar effect. For example, the patient's menopause will probably be more severe and dangerous than most. In addition to the usual adjustment problems, the menopause would relate to her reaching an age where giving birth to the rival sister is no longer possible. As such, this phase of her life would be equated with the revival of her conflicts over her wish to destroy her sister. With it lies the danger of her turning the impulse against herself as she did in the past.

Finally, it should be understood that our knowledge of this patient is quite incomplete and that the development of any psychiatric symptoms, especially those related to depression, should be regarded with the utmost seriousness, regardless of any life situation context.

Summary

The difficulties of accurate clinical evaluation vary in different medical and psychiatric situations. One of the most difficult and dangerous is that in which the physician suspects some risk of a suicide attempt. This difficulty is so great, not only because of the multiple etiologic and environmental factors at work, but also because the patient may be unaware of his suicidal intentions or be aware of them and conceal them from the physician.

The present paper offers no easy solution to this problem of clinical judgment. It does offer some areas in which exploration and questioning may be directed in order to add to the available data, lead to a more accurate appraisal, and, by so doing, hopefully reduce the frequency of unnoticed suicidal intentions.

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Acid-Base Changes in Renal Dysfunction following Open Heart Surgery

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Abstract

Renal dysfunction following open heart surgery can be diagnosed in the early postoperative period by sequential determination of the free water clearance much before any rise in the BUN becomes evident. The presence of a less negative free water clearance in the postoperative period indicates renal dysfunction and a high probability of developing acute renal failure. These patients also have significant early differences in their acid-base balance. They have a greater degree of metabolic acidosis during and immediately following cardiopulmonary bypass and later in the postoperative period they develop a more marked and longer lasting metabolic alkalosis. Careful monitoring of the free water clearance and acid-base status during and after open heart surgery allows recognition of those patients with borderline cardiac function that are likely to develop renal dysfunction.

Introduction

Renal dysfunction (RD) following open heart surgery continues to be associated with a very high mortality rate even when postoperative therapy is aggressive (1, 2, 3). Although multiple factors have been implicated, the etiology of RD remains unclear. The diagnosis is usually not made until the third or fourth postoperative day when the blood urea nitrogen (BUN) and creatinine have become clearly elevated or when the patient has become severely oliguric or anuric. We have found that open heart patients who develop RD (defined as a rise in the postoperative BUN to more than 50 mg%) are less able than other patients to concentrate their urine and cannot maintain as negative a postoperative free water clearance (FWC)* as other patients (5). These differences are generally significant in the first hours after surgery, much before any elevation in BUN or creatinine, and may occur in the absence of any significant change in urine output, blood pressure or left atrial pressure. The purpose of this study is to compare the changes in acid-base parameters of patients who developed postoperative RD with those that did not to determine if differences might correlate with changes in FWC and thus provide additional early warning of RD.

Methods

Forty consecutive adult patients who underwent open heart surgery using a hyperosmolar perfusion prime were studied.

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* C_{H_2O} (4)

Eight of these developed a postoperative BUN over 50 mg%. They were compared to 30 patients that did not have such BUN elevation. Two other patients were excluded from the study: One was on dialysis preoperatively for chronic renal failure and the second developed a diabetes insipidus like syndrome immediately after surgery followed by renal failure two weeks later. Patients received 0.3 molar THAM (tromethamine) solution during CPB as needed to correct any acidosis. THAM administration was discontinued following termination of cardiopulmonary bypass (CPB).

Samples for blood gases and acid-base analysis were collected from an indwelling radial artery cannula at the intervals given in Table I. Blood gases were analyzed immediately after collection. Following determination of the arterial pH, the pH_{40} (6) was measured after equilibration of the blood sample at a pCO_2 of 40 mm Hg. The pCO_2 and base excess were then derived from the Siggaard-Andersen Nomogram (7). The arterial pH was corrected to the temperature of the patient. The urinary osmolality (Uosm), urine volume (Uvol), and plasma osmolality (Posm) were measured following induction of anesthesia and at intervals nearly simultaneous with the pH values and blood gases. The free water clearance was calculated by subtracting the osmolal clearance from the urine volume by the formula:

$$\mathrm{FWC} = \mathrm{Uvol} - \frac{\mathrm{Uosm} \times \mathrm{Uvol}}{\mathrm{Posm}}$$

where the clearances and volumes are in ml per minute and the osmolalities are in milliosmoles per kg.

Results

There is no statistical difference in the preoperative blood gases, urinary osmolality, FWC, BUN or creatinine between the 30 patients that served as controls and the 8 that developed RD. Figure 1 shows the mean FWC in the two groups of patients. After an immediate rise in the negative FWC, when the patient is placed on CPB, there is a drop with return to near prebypass

TABLE I

Description of the time intervals at which samples were collected

Pre-CPB	1	Immediately before anesthesia
	2	30 min after induction
CPB	1	10 min on bypass
	2	60 min on bypass
Post-CPB	1	10 min postbypass
	2	40 min postbypass
	3	2 hours postbypass
	4	3 hours postbypass
	5	6 hours postbypass
Days Postop	1	First postoperative day
	2	Second postoperative day
	3	Third postoperative day

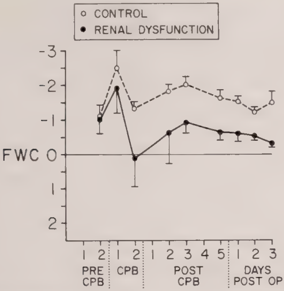
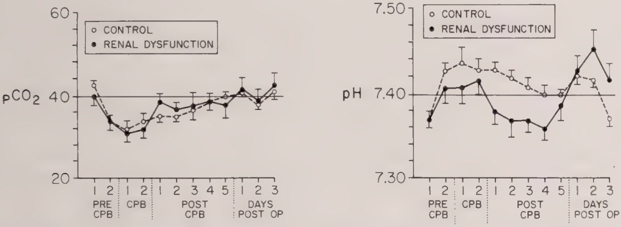


FIG. 1. Mean free water clearance (FWC) in the two groups of patients. The dashes represent the standard error of the mean. The time intervals are given in Table I. The FWC becomes positive after one hour on CPB in the renal dysfunction (RD) patients and remains less negative throughout the remainder of the study. See text for details.



FIGS. 2 and 3. Comparison of mean pCO_2 and pH values. There is no significant difference in the two pCO_2 curves. The pH plots show that the RD patients develop a temporary acidemia after CPB, followed by a more marked alkalemia than that present in the control patients. See text for details.

levels in the control patients. This decline is more precipitous in the RD patients and the FWC reaches a mean positive value of +0.1 ml/min ± 0.9 SEM. There is a recovery period following CPB with a secondary rise in the negative FWC in both groups. The negative FWC in the RD patients, however, rises more slowly and returns only to prebypass level ($P < 0.05$ at 2 hrs. after CPB). Subsequently the negative FWC gradually drops, returning to prebypass levels by the second postoperative day in the controls. In contrast, in the RD group it approaches zero as the BUN and creatinine gradually increase.

Figures 2 and 3 show the arterial pCO_2 and pH values in both groups of patients. There is no significant difference in the two pCO_2 curves. The pCO_2 declines with the onset of anesthesia, remains low during CPB, and then gradually returns to normal in the first 6 hours post CPB. In the control group the pH rises initially, indicating an alkalemia prior to and during CPB. There is a return to baseline in the early postoperative period and then a secondary mild alkalemia lasting several days. The RD tracing parallels the control group,

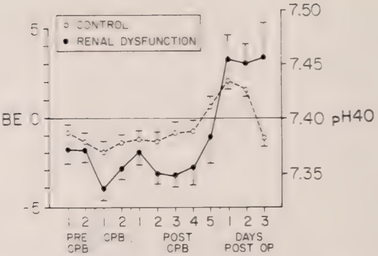


FIG 4. Base excess (BE) and equivalent pH_{40} values. The RD patients develop an acidosis during CPB which is temporarily corrected by the administration of THAM during bypass and then the acidosis returns. These changes are not present in the control group. Later postoperatively, the RD patients show a more marked and longer lasting alkalosis.

but shows less alkalemia during anesthesia and CPB, with a larger drop in pH (acidemia) post-CPB ($P < 0.05$). There is a more marked late "rebound" alkalemia in these patients. Figure 4 shows the contemporary metabolic changes, represented by the base excess (BE) or the pH_{40}. Except for a slight decrease at the onset of CPB, they are close to normal during surgery and the early postoperative period in the control patients. Later postbypass there is a temporary rise, resolved by the third postoperative day, representing a mild alkalosis. The RD patients show essentially an exaggeration of this pattern. With the onset of CPB is a more marked acidosis (decrease in pH_{40} or BE) which then gradually returns to the normal range concurrent with the administration of THAM ($p < 0.05$). After the end of CPB, these patients no longer receive THAM and there is a second drop in the pH_{40} or BE which lasts for several hours with a gradual return to prebypass levels by 6 hours ($p < 0.05$ at intervals, 2, 3 and 4 post-CPB). The late rebound alkalosis is more pronounced and longer lasting.

Discussion

Renal function, as measured by the FWC, is well maintained during CPB if there is adequate tissue perfusion. A less negative FWC (or positive FWC) post-CPB signals a probable low cardiac output syndrome and RD long before there is a significant decrease in the urine volume of rise in the BUN and creatinine. This is now recognized as a useful early warning signal (5, 8). The present study shows that changes in FWC are paralleled by changes in acid-base balance and that these are also predictive of low cardiac output syndrome and RD. The patients that have an earlier and more marked metabolic acidosis require more antacid to correct the acidosis and show a more pronounced and persistent late metabolic alkalosis.

The absence of a good cardiac output after CPB for cardiac surgery may be the most important factor in the etiology of RD. The osmotic diuresis during hyperosmolar CPB does not prevent renal damage, but does provide a false sense of security by producing a large urine output. Variations in FWC are more indicative of the quality of renal function and hence much more predictive than urinary volume or osmolality alone. This is especially true since the urinary output will not decrease markedly in the presence of a strong osmotic diuresis unless there is a severe decrease in the renal perfusion (9).

Careful monitoring of serial acid-base changes and FWC during and immediately after CPB will facilitate early recognition of those patients with borderline cardiac function even though they are neither hypotensive nor oliguric. These are the patients that will develop RD and from this group come those who later develop frank acute renal failure. They may now be recognized several days before the BUN and creatinine elevations become significant. Timely recognition will allow for corrective measures to be undertaken in the early postoperative period.

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The Use of the Problem-Oriented Medical Record in Two Centers

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Introduction

The Problem-Oriented Medical Record (POMR) is an easily applied method for arranging complex medical data. It has been slow in being accepted because it is radically different from the traditional medical record. The Veterans Administration recently decided to introduce POMR and the decision has affected the Mount Sinai surgical training program at the Bronx Veterans Administration Hospital. At about the same time the Professorial Surgical Unit at St. George's Hospital in England also decided to study the use of POMR in action. This was organized by the author who has been able to observe POMR for about a year in each of the two centers.

Three things were clear. First, POMR could not succeed unless the entire department understood and embraced the concept. Second, the physician who was able to write a good complete traditional medical record did not need-POMR, but lesser mortals whose record-keeping was poor and would have benefited greatly from POMR, could not cope without extensive training. Third, the problem list was by far the most valuable spinoff from POMR since it was a major timesaver in checking a patient's history when kept continually up to date.

Method

The POMR was developed by Dr. Lawrence Weed (1) who saw that any physician may easily be overwhelmed by a mass of apparently unsifted data. Initially, his concepts were embraced in full at the Bronx Veterans Administration Hospital even to the extent of providing data sheets that the patients were able to complete, in order to give their own histories. These were largely ignored by the surgical residents possibly because the Weed system looked to them like so much extra paperwork. Weed had intended to improve teaching and clinical care through problem definition and solution. At St. George's it was decided to modify the Weed approach and perhaps simplify it so that it remained akin to the traditional record, in the hope that it would be easily accepted.

Any medical record starts with the Data Base that essentially comprises the standard history, examination, and investigations. In all cases, but particularly using POMR, it was helpful to preface the medical record with a sentence which included date and reason for admission and in particular the first

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impression gained by the doctor of the patient, e.g.: "9/9/76 patient admitted because of abdominal pain. Collapsed old man."

Of course the Problem List was the key to the POMR and it needed to be made out as the patient's data base is compiled, that is, when the patient was first seen. A problem was stated as precisely as it could be in the light of information available at the time, and as each one was identified it was given a number which should be in chronological order on the problem sheet. This number remained unaltered and could be used henceforth in the chart whenever that particular problem required action. When a problem was difficult to identify, it was better to discuss the matter with the staff rather than to state it inaccurately; sometimes it was not possible to recognize a problem at all until more data became available. Then it could be added to the problem list which acted as a continually updated index of the patient's file and was placed as the first sheet of the chart.

It was important that the problem list was continually updated, not only by adding new problems, but also by more accurately defining those already entered. For example, problem number 1 may be "1966, appendicitis—appendectomy" with problem number 2 as "4/76, abdominal pain." After the initial plans have been carried out, the raised serum amylase and positive methaemalbumin would allow a change of title to "hemorrhagic pancreatitis."

Problems were classified to include the following: a past illness; an allergy, including drug sensitivities; a physiological entity or syndrome; an operation, past or present; treatments involving risk (e.g., steroids, anticoagulants, immunosuppressives); a risk factor (e.g., smoking, a psychological or social problem); a symptom; a sign; an abnormal investigation result; a proven diagnosis. Some of these problems were solved, and became inactive (e.g., "abdominal pain—appendicitis—appendectomy") and some remained active because of long-term sequelae (e.g., diverticular disease).

The problem list was not complete without dates, and dates of the first clinical observation, dates of operations, and of change or solution, were entered when they occurred.

After the data base and problem list were completed, initial plans were made and carried out. Another way of saying this is that after the case notes were made out, routine investigations were performed and then indicated lines of investigation were followed.

Progress Notes were written using the SOAP format outlined below, each entry being written under the number (and title) of the problem to which it referred. After rounds, the charts were updated and the SOAP format followed thus:

S— Subjective information—what the patient says
O—Objective information—examination findings; investigation results
A—Analysis—the doctor's assessment of the available evidence
P—Plans—what the doctors have agreed to do.

This includes diagnosis (Dx), therapy (Rx) and a record of what the patient is told about the illness (Ex).

All entries were signed and the rank of the signator included.

The Final Progress Note was most important because it should direct the course of continuing management of the patient's problems, each of which should be briefly reviewed, solutions should be indicated and arrangements made for disposal and follow up clarified. This was of particular help to the resident who was responsible for the discharge report which could be replaced verbatim by the final progress note when dates, numbers and titles of the problems were included.

Discussion and Results

The traditional medical record was analyzed by Feinstein (2) who indicated that it was arranged haphazardly as a result of its chronological sequence. Hence data is difficult to analyze because it is difficult to find and there is much time wasted perusing the entire record; consequently the analysis can be quite unreliable and inconsistent. Too much reliance has to be placed on memory simply because the traditional medical record cannot effectively handle the information generated by our increasing capacity to sustain and preserve life. Many old problems remain to be solved but the increasing complexity of medicine, its ultraspecialization and its increasingly potent therapeutic armamentarium cause newer problems. Up to 20 percent of hospital admissions in England result from iatrogenic disorder (3); environmental, social, and epidemiologic factors have tended to be omitted from the traditional record and problems that do not "fit in" have been ignored. Also, as educational tools medical records are failing because the rules are haphazard and there are no standards by which they can be judged.

Weed's approach (1) was to orient data around problems that could be analyzed and defined, thus leading to a greater understanding and hence solution, so that clinical care and teaching could be improved.

In taking up the idea, Hurst (4, 5) has made the following observations: POMR encouraged logical thought, itself educational. The display system of the POMR was as efficient in use as a dictionary. Information was readily available to all auxillary personnel so that management, understanding and experience was improved. Clinical investigation was used with strict economy and today this is increasingly relevant. The attending was better able to check the patient's medical problems and his residents were better able to record and interpret data. In addition to improved postgraduate training POMR met the requirements of integrated clinical and preclinical courses for logic in establishing each problem through a study of etiology, altered anatomy, physiology and function. It could be used to construct algorithms so that auxillary staff could collect data and act within defined limits. This logical approach was compatible with computer recording.

Experience in the two centers showed that, despite excellent theoretical reasoning, there was a reluctance toward the use of POMR. This may be explained by the fact that it reduced emphasis on those basic skills in diagnostic judgment which have been inculcated in training. Difficulty was experienced by residents in problem formulation and indeed at the Bronx V.A. Hospital the problem list was usually ignored until at, or after, the discharge date and so it became a chore. This followed from the standard routine of making a list of differential diagnoses and putting one of them down as a problem later, and the increasing tendency to write down a diagnosis as, "rule out cancer," for example. Sometimes, "rule out cancer" has been put down as a problem. Indeed it is a problem, but it is the doctor's problem and not the patient's. When cancer has been "ruled out" then that has sometimes been the end of the matter but the patient's real problem, abdominal pain, has continued.

On the positive side, once the concept was grasped that the notes have to be written with clinical problems in mind, and that those encompass diagnosis, the task became simple. In addition, it was found at St. George's that when the Professorial Unit as a whole considered and checked the problem lists on rounds, a closer unity of purpose was also achieved. The orderly presentation of material in the problem lists and the assessments within the SOAP format gave other disciplines at resident and staff level a readily assimilable source of information when seeing a patient on referral. At St. George's Hospital this resulted in a favorable reaction from residents outside the unit who wanted to take up POMR but the staff was reluctant to participate. Surprisingly, it has been the other way around at the Bronx V.A. Hospital, with residents taking the conservative line rather than attendings. Those using POMR have found there has been considerable assistance in planning conclusions and following those plans through in outpatients.

The educational value of POMR has been discussed and this was put into practice at St. George's in that students attached to the Surgical Unit prepared their case notes on these lines. By having to formulate problems which depended on the individual patient rather than on diagnosis and having to define their assessments, they felt that it was a valuable exercise in developing clinical judgement.

On both sides of the Atlantic, the Medical Records Departments have been more than willing to participate in POMR, probably because a review of the problem sheet made tabulation of results a much simpler task. In such a case, more accurate statistics become available, probably over a wider range of material leading to greater correlation of findings which can improve research and teaching.

Conclusions

The problem-oriented medical record is an improvement on traditional record keeping but involves such a change in attitude that it seems unlikely that it will be accepted in the near future. This should not prevent newer generations of physicians from being taught a superior method of record-keeping from the outset.

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Multiple Halothane Anesthesias in a Child: A Case Report

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Halothane anesthesia repeated at short intervals is considered to be the main factor in post-halothane liver dysfunction. This is believed to be a hypersensitivity reaction (1). Inman et al found a decreasing latent period in nine patients with more than one episode of jaundice following exposure to halothane (2). They postulated that an accelerated immunological response is implicated in the development of post-halothane hepatitis.

We present a pediatric patient, who for 3½ years received halothane at such short intervals that during each successive anesthesia he still retained halothane from the previous exposure (3). The fact that hepatitis did not occur in this setting is important in adding to our knowledge of the syndrome of post-halothane hepatitis.

Case Report

A diagnosis of esophageal atresia, with a tracheo-esophageal fistula, was made on the day of birth, in this otherwise healthy baby. Gastrostomy was performed on the following day. Studies showed a short lower esophagus, and primary anastomosis was not attempted. Cervical esophagostomy was performed at the age of six weeks.

A colon interposition was performed when the patient was aged eleven months. A cervical anastomotic leak complicated his postoperative course, and persisted for about six weeks. At this time swallowing became more difficult and esophagoscopy was performed. Retrograde dilatation of the esophagus, via the gastrostomy, was performed one month later and repeated at intervals of 5–60 days. Occasionally the patient also required esophagoscopies for removal of impacted food. At the age of 3 years and 9 months, an esophageal silastic prosthesis was inserted after dilatation of the graft. After a trouble-free period of 5 months, when two esophagoscopies showed mild esophagitis, a sudden return of difficulty in swallowing occurred. Esophagoscopy showed an alarming degree of inflammation and the silastic stent was removed. Attempts to control the postinflammatory stenosis with triamcinolone injections failed.

He then underwent a second conduit procedure, using a gastric tube. The patient underwent a total of 54 halothane anesthesias. He was exposed to halothane for each surgical procedure for 30 to 45 minutes, with the exception of the longer surgical procedure of colon interposition and the second conduit procedure which lasted approximately four hours. Suxamethonium was given on a few occasions to facilitate endotracheal intubation. Anesthesia was maintained with oxygen, nitrous oxide and halothane. The patient was intubated to avoid aspiration during esophageal dilatation and esophagoscopy. Vital signs remained normal during all procedures. Extubation was easy and without respiratory difficulty. The exposures on average were repeated at intervals of fifteen days. Postanesthesia recovery was uneventful, occurred within thirty minutes, and the patient was fully awake, walking, and feeling well enough to be discharged home after two hours.

At no time was the patient jaundiced. The liver chemistries, performed on two occasions, were within normal limits.

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Discussion

Age has been accepted as one of the possible contributory factors of post-halothane hepatitis. Middle-aged people show a higher incidence and the general opinion exists that only rarely do children develop this type of hepatic disease. The National Halothane Study (4) found that the rate of massive hepatic necrosis following all types of anesthesia was lowest in the youngest age group and highest in the oldest. McCollum (5) reported all types of hepatitis are commoner and more severe in older persons. This would favor the view that factors other than halothane are responsible for liver dysfunction following halothane anesthesia.

Children constitute almost 12% of the surgical population, and with few exceptions, all pediatric patients are anesthetized with halothane, nitrous oxide and oxygen. This indicates that the vast majority of pediatric surgical patients are exposed to halothane. If one considers that 70% of adults receive general anesthesia and of these one 50% receive halothane, the percentage of children exposed repeatedly to halothane, is not significantly different from that of adults. Thus, if the percentage of children exposed to halothane approaches that of adults, the reported cases of post-halothane hepatitis should also be in the same percentage range. This however is not so. If post-halothane hepatitis exists in children, it is so rare as to be virtually nonexistent. In our hospitals we use halothane extensively for pediatric cases and our average pediatric case load is 3000–3500 cases yearly. In reviewing those of the last seven years, we have yet to find a single case of post-halothane hepatitis in a child.

Several cases of jaundice in pediatric patients following halothane anesthesia are described in the literature (6–11). All can be ascribed to causes more common than post-halothane hepatitis. In addition, Smith (12) did not report a case of "Halothane hepatitis" in his paper on anesthesia for surgical correction of strabismus. He reported on over 3000 cases in a five-year period. The author stated, that he avoided halothane in patients with known or suspected liver disease, and that other inhalational agents offered no advantage over halothane.

Sherlock (13) has observed that the newborn has a sensitivity to drugs different from that of the adult. Drugs such as novobiocin and salicylates can cause jaundice in the newborn, but not in the adult. Fouts and Hart (14) were unable to induce hepatotoxicity in newborn animals exposed to enzyme-inducing agents or halothane anesthesia itself, presumably due to immaturity of enzyme systems responsible for metabolism of drugs. Chang et al (15) reported ultrastructural changes in the fetal liver of animals exposed in utero to halothane. However, one important factor is species difference, and existing data indicate that caution must be exerted when information obtained in subhuman species is applied to man. Corssen (16) using phase-contrast-time-lapse microcinematography was able to observe and record drug-induced morphologic cellular alterations of nuclei, nucleoli, cytoplasm and cytoplasmic activity. Human liver cells were cultured in appropriate nutrient and exposed to anesthetic concentrations of halothane (52mg/100ml). At no time could the author demonstrate disturbances of morphologic or cytoplasmic function. On the contrary, when the nutrient was deficient in protein or carbohydrates, halothane caused slight to moderate damage.

It has been suggested that the sporadic and unpredictable occurrence of most hepatotoxic drug reactions can be explained either by genetic variation or hypersensitivity produced by an immunologic reaction (17). Arias provided circumstantial evidence that drug hepatotoxicity in man might on occasions be determined genetically (18). He observed chlorpromazine jaundice in three members of the same family. We know that humans metabolize more halothane than other species, and that the amount of nonvolatile urinary metabolites is higher in fraternal twins than in identical twins (20). This suggests a greater influence of genetic than environmental factors in the metabolism of halothane. However, no case of hepatitis following halothane has been reported in two or more members of the same family, which would allow us to propose a genetic factor being involved in the development of "halothane hepatitis."

Children are known to be less prone to allergy than adults (21). This has made many to believe that the rarity of halothane hepatitis in this age group is a result of immunologic immaturity. Yet, attempts to explain halothane hepatitis on the basis of an immune reaction have failed. In a group of patients with unexplained hepatitis following halothane anesthesia, there was an increased incidence of thyroid antibodies (in the absence of thyroid disease). This, together with an increase in liver and kidney microsomal antibodies, is further evidence that these two autoimmune responses are often associated (22). It is possible those who are prone to develop organ-specific autoimmunity are more liable to develop hepatitis following halothane anesthesia. However, three of five patients with unexplained hepatitis following halothane, did not develop jaundice on being reexposed to halothane. Walton (22) exposed lymphocytes from patients who had histories of jaundice following halothane exposure in order to artificially produce conjugates of trifluoroacetate with liver specific protein and human serum albumin. The authors looked for lymphocytic transformation and inhibition of leucocyte migration to obtain evidence of cellular hypersensitivity to these antigens. They found no in vitro cell-mediated immunity in these patients and no evidence in favor of such a hypothesis. In addition, volunteers anesthetized with halothane for six to eight hours showed no alteration in lymphocyte transformation (24), which indicates that halothane alone does not interfere with the immune responses.

Conclusion

A pediatric patient is presented with multiple exposures to halothane anesthesia without evidence of post-halothane liver dysfunction. Available evidence, which we have reviewed, supports neither a decreased hypersensitivity reaction nor immunologic immaturity as an explanation of the extreme rarity of post-halothane hepatitis in the pediatric age group.

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Improved Quality and Continuity of Outpatient Care with the Use of a Nurse Practitioner—A Study of Adult Women Patients with Urinary Tract Infection*

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Introduction

For many inner city residents, the emergency room (ER) has become a primary care clinic rather than an accident ward. In a large number of institutions, this evolution has not been accompanied by an improvement in the ability to deliver continuing care for nonacute problems. When quality has been assessed in terms of patients' returning for diagnostic x-rays (1), further evaluation of chest pain (2), abdominal pain (2), hypertension (3), and a wide variety of medical problems, continuity of care is poor and quality suffers.

The use of well-trained nurse practitioners, physicians' assistants, medexes and follow-up clerks can improve the quality of care offered in an ambulatory setting (4–9). These nurses and paramedics are particularly useful in following-up patients whose illness requires a second visit. When care is provided by the same practioner, the sustained rapport may improve the patient's compliance for follow-up and the practitioner fulfills his or her commitment to see the patient's initial problem correctly resolved.

At The Mount Sinai Hospital women seen in the ER for urinary tract infections (UTI) are referred for their followup to another clinic and another doctor. No single physician or nurse is responsible for the patients' continuing care, and attendance at the scheduled followup clinic has been poor. We have performed a small, randomized trial to determine whether nurse practitioner intervention can improve the quantity and quality of care currently provided to these patients.

Background

The emergency room of the Mount Sinai Hospital handles 54,000 visits per year from adults living primarily in the neighbouring East Harlem community. Women presenting with complaints referable to the urinary tract (dysuria, polyuria and flank pain) are seen by the members of medical house staff who evaluate the patients' complaints, initiate therapy, and make a referral to some

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other clinic or physician for follow-up care. If the patient has a private physician or attends a medical clinic at the hospital, she is referred there for further care. Otherwise, the patient is sent to female genito-urinary (GU) clinic for a repeat urinalysis, urine culture and whatever diagnostic evaluation may be required. Laboratory results from the emergency room are sent to the record room to become part of the patient's permanent chart. The chart follows the patient to all clinics and is a record of the care the patient receives from the hospital.

Methods

All urine microbiology reports from the emergency room during a two and a half month period were screened for evidence of a urinary tract infection, defined as the presence of 100,000 organisms or more per ml. on quantitative culture. Cultures growing multiple organisms were included if one of the organisms was a known pathogen, and cultures growing exclusively nonpathogens (e.g. diphtheroids, S. epidermidis) were excluded. The patient's age and sex are recorded on the same laboratory slips so adult women of 20 or more years of age could be specifically selected for inclusion in this study. Laboratory data including urinalysis and antibiotic sensitivity results were collected for all patients.

The sample was randomized and patients whose hospital identification numbers ended in 2, 3, and 8 served as controls. All others (the intervention group) were contacted by a nurse practitioner (RR) who arranged and encouraged the patient to return for a followup visit. Two months after the first emergency room visit, the hospital record of each patient was reviewed for information concerning their followup. Charts not available from the record room were requested weekly for three successive weeks. All patients who had not returned to the GU clinic were queried by questionnaire administered by letter or by telephone to determine whether or not they had received adequate followup care. In this study, adequate followup care is defined as a patient being seen again by a physician who performed a repeat urine culture within two months of the original complaint.

Results

Registration

During a two and a half month period, 56 women with positive urine cultures were seen in the ER. Their ages ranged from 20 to 89 years with a mean of 39 years. We were surprised to find that 21 (38%) of these patients were hospital employees who are generally expected to attend the employee health service clinic at the hospital.

The 56 positive cultures included 39% with E. Coli, 20% with enterococci, 14% with Klebsiella and 12% with multiple organisms and 15% with other organisms. 53% of the patients were not prescribed any antibiotic in the emergency room. Of those who received an antibiotic, only half were prescribed a drug which was effective in vitro against the infecting bacteria.

Randomization, Intervention and Follow-up

Upon randomization, 32 patients were allocated to the intervention group and 24 patients to the control group. There was no significant difference between these groups by age, pay status or initial use of antibiotic.

Fifteen patients in the intervention group returned to the G.U. clinic for follow-up; only 3 from the control group were seen again. This difference is significant ($P < .01$) and can be attributed to the nurse practitioner's intervention (Table 1).

Charts of 26 (85%) patients in the intervention group and 19 (79%) in the control group were available for review (Table 2). The adequacy of follow-up for patients who had returned to the G.U. Clinic or to other hospital clinics was obtained from the chart; 25 of the 26 patients in the intervention group but only 3 of the 19 patients in the control group received adequate follow-up care in the hospital. Since the patients came to the emergency room for their complaints, much of their follow-up care—if received—should have occurred in the hospital and have been noted in the hospital record.

Seventeen patients in the intervention group and 21 patients in the control group who had not returned to the G.U. Clinic for follow-up were sent a questionnaire by mail. Nonrespondents received a second questionnaire and were subsequently called by phone. Eleven patients were successfully contacted in each group and their responses to the questionnaire were the same: five returned to see another physician who had performed a repeat urine culture.

Combining these results, evidence for adequate follow-up was available for 25 (96%) patients in the intervention group and 5 (24%) in the control group.

TABLE I

Effect of Nurse Practitioner's Intervention to Encourage Followup of Patients in the Female G.U. Clinic

Intervention	G.U. Clinic followup		Total
	Yes	No	
Nurse Practitioner	15	17	32
None	3	21	24

$P < .01$.

TABLE II

Evidence of Adequate Followup (FU) of Urinary Tract Infections among Women seen in the Emergency Room

Group	Chart review				Questionnaire response				Summary of FU information		
	N	Charts found N	Adequate FU		Sent no.	Response no.	Adequate FU		Some FU information available N	Adequate FU	
			Yes	No			Yes	No		Yes	No
Intervention	32	26	25	1	17	11	5	6	31	25	6
Control	24	19	3	16	21	11	5	6	21	5	16

Discussion

To avoid the long-term complications of UTI's, good medical practice demands that these patients receive an antibiotic on their initial visit which should be adjusted according to the culture and sensitivity results and should have a sterile urine culture performed at the completion of therapy (10). This study has assessed the quality of care provided in the emergency room as measured by the choice of appropriate initial antibiotic and the ability of a patient to have her urine checked in follow-up. 53% of patients in this study were prescribed no antibiotic at the first visit and of those receiving an antibiotic, only half had organisms sensitive in vitro to the drug prescribed. Neither of these measures of quality would be valid if the patient had been successfully recalled early for review of her treatment. In the control group, appropriate follow-up could be documented for only 5 patients although an admittedly large group was lost to follow-up and only 3 of the 19 patients for whom charts were available ever returned for their follow-up appointment. "Intervention" led to a significant increase in the rate of follow-up.

In other institutions, protocol management of UTI's by nurse clinicians with physician back-up has been used to provide quality care at initial presentation (11, 12). Follow-up clerks have been successfully employed to encourage patients to return when required (9). The use of a nurse practitioner at our institution to provide some initial care and all follow-up care to patients with UTI could improve the quality of care provided to our out-patients.

Specifically, a nurse practitioner responsible for female UTI's could

1. Make sure all available data (urinanalysis, urine culture and sensitivity) are recorded in the patients' charts; More than 20% of the data is currently not available in the patients' records.
2. Be more aggressive in recalling patients whose urine was initially contaminated (more than 12%) or in reviewing the antibiotic prescribed when the organism was not sensitive to it (50%).
3. Be responsible for the complete follow-up of these patients until their repeat urine culture is sterile. Only 12.5% of patients in the control group returned for their original follow-up appointments.
4. Participate in staff education in the treatment of UTI and other outpatient illnesses which require follow-up visits.
5. Encourage employees (38% of total patient group in this study) to obtain their care from the employee health services provided to them.

Fragmentation in the care delivered to patients with UTI in the emergency room diffuses responsibility for the patient from the first physician of record to the institution as a whole. The utilization of a well-trained nurse practitioner in the treatment and follow-up of these patients provides a practical alternative for the delivery of quality care in this outpatient setting.

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A Drug Use Index Approach to the Evaluation of Antibiotic Utilization*

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Introduction

Much attention has been paid in the literature to the overuse and misuse of drugs in medical practice, with particular attention often focused on the antibiotics (1). While it is in vogue to look carefully at drug utilization in light of the need for hospital cost containment, this should not eclipse the fundamental problem which is the "direct connection between prescribing that fails to meet sound therapeutic criteria and the shortcomings of our system of drug information" (2).

For example, using a sociologic approach, Becker et al found that physicians prescribe a wide variety of drugs, including antibiotics, for common illnesses and complaints, for poorly diagnosed conditions, or for illnesses for which there is no satisfactory and generally accepted treatment (3).

Two independent studies have shown that more than half the inpatient use of antibiotics was inappropriate or erroneous (4, 5). It was found that patients received antibiotics without definitive evidence of infection or in the absence of bacteriologic data. Frequently an inappropriate drug was administered or the drug was prescribed in the wrong dose or for an improper duration. In addition, contraindications for antimicrobial therapy such as patient allergy were occasionally ignored.

City Hospital Center at Elmhurst is an 816-bed institution operated by the New York City Health and Hospital Corporation and is a major affiliate of The Mount Sinai Medical Center. In 1975, because of the fiscal crisis in New York City, the Elmhurst Hospital budget was reduced. A Program and Budget Reviewed Committee was formed to establish priorities and to help allocate budget reductions recommended the development of a program to reduce the use of frequently misued high-cost drugs.

This paper reports on the implementation of the committee's recommendations through a sequential series of policies and their effect on the use of the cephalosporin antibiotics. A Drug Use Index (DUI) was developed to compare the use of different antibiotics so that information could be fed back to the clinicians. While it was assumed that the heightened awareness would result in more appropriate antibiotic utilization, it was found that an unanticipated

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consequence of cephalosporin control was a corresponding increase in the use of other antibiotics.

Context

Brodie et al (6, 7) have identified five criteria for assessing the efficacy of a drug utilization review program. They define drug utilization review as "an authorized, structured, and continuing program that reviews, analyzes, and interprets patterns (rates and costs) of drug usage in a given health care delivery system against predetermined standards."

The criteria are:

1) Authority: recognition of the continuing nature of the program and the allocation of the resources and sanctions required to sustain it;
2) Knowledge of operational characteristics of the delivery system and demographic characteristics of the population served (e.g., background and training of physicians and pharmacists in the system, population mix and hospital utilization patterns);
3) Existing profile of drug utilization (e.g., incidence of adverse drug reactions, drug utilization for selected categories of patients);
4) Model treatment criteria (drug utilization criteria for specific diagnoses); and
5) A schema to assess changes in cost and rates of utilization and the benefits of the program.

According to this model, a drug usage review program should accomplish four ojectives: the level of patient care should be maintained or improved; hospital resources should be used more effectively; the pharmaceutical services should become better integrated with other hospital services; and finally the program should have the capability to evaluate drug utilization.

Several examples of drug utilization programs have been reported in the literature, including the limitation or restriction of the availability of selected antibiotics by changes in the hospital formulary (8), the combination of drug sensitivity reports with antibiotic utilization data to educate users (9), and the provision of computerized consultation to physicians for infectious disease therapy (10).

Elmhurst Drug Utilization Review Program

The Elmhurst Drug Utilization Review Program initially focused on the cephalosporin antibiotics because they are heavily used and consume a substantial fraction of the pharmacy budget.

Phase I of the program was a drug restriction and cosignature policy. The policy required that senior attending physicians cosign all orders for a cephalosporin antibiotic within 24 hours after the therapy was initiated. It was felt that supervision by attending physicians would require house staff to exert more care in antibiotic selection and would serve as a mechanism for house staff education.

For the first few weeks following the implementation of the policy, the use of cephalosporins was reduced. This system required the continuous attention of the attending staff who found the extensive documentation and case review to be tedious and time-consuming. Following the initial impact, the attending staff vigilance declined and utilization slowly returned to prepolicy levels. However, since a dramatic reduction had been achieved, par stock levels were established based on the period of highest success during the cosignature policy period.

Because a policy requiring much effort on the part of the practitioners lost its effectiveness in a short time, it was decided as part of Phase II that a data base of antibiotic use would be developed to streamline the system. A weekly report providing data on cephalosporin use by ward, indicating grams used, total cost, and cost per patient day was distributed to the Directors of Service (Table I). An analysis including unusual trends or usage was also distributed. The purpose was to give the directors comparative data with which they could monitor drug use in their own departments.

In order to evaluate the effect of the Phase II policy, a Drug Use Index (DUI) was developed. This index is calculated by dividing the quantity of the drug used per month by the average daily dose and the average daily census for the same period.

$$\text{DUI} = \frac{\text{drug used}}{\text{average daily census} \times \text{average daily dose}}$$

This index has the dimension of drug days per patient. The DUI makes it possible to directly compare use of different antibiotics while correcting for the expected seasonal variations of hospital census. The estimated average drug dose used in the calculation of DUI is contained in Table II.

TABLE I

Cephalosporin antibiotic use for the week ending 8/21/77 (Abstract Report)

Service/Ward	Beds	Grams Used	Total Cost	Cost Per Patient Day
ICU	15	70	$ 186.70	$2.01
Surgery				
A4	38	90	216.90	1.15
B4	41	186	376.76	1.79
E4	35	84	212.24	1.16
A5	41	6	18.66	.09
B5	30	148	290.78	1.54
Total	185	514	$1115.33	$1.15
Medicine				
A6	41	45	72.70	.27
B6	41	38	111.18	.48
A7	42	93	261.93	1.10
B7	42	20	48.20	.19
Total	166	196	$ 494.01	$ .34
OB-Gyn				
A8	31	108	205.94	1.13
B8	25	101	211.86	1.59
Total	56	209	$ 417.80	$1.34

The report was circulated beginning June 1977. The quantities of injectable antibiotics used per month were obtained over the 21-month period from January 1976 to October 1977.

The effect of the Phase II policy on the DUI for the major antibiotics was evaluated by the use of regression analysis compensating for first-order autocorrelation with the two-step Durbin procedure (11).

Results

The DUI estimate for the cephalosporins for the nonpolicy period was 1.01 drug days per patient which dropped to 0.67 (Table 3) after introduction of the policy. Figure 1 graphically depicts the changes in drug utilization during the entire study period. The implementation of this policy resulted in an expected 32% reduction of cephalosporin use during the policy period compared to the nonpolicy period ($P < .01$). The combined use of the aminoglycosides and the cephalosporins was not affected by the drug use report policy ($P > .9$). It was not anticipated that the implementation of this program would result in an increase of the aminoglycoside DUI by 77% compared to the non-policy period ($P < .01$). There was no effect on the use of penicillin congeners by the policy ($P > .9$).

TABLE II

Estimated average daily dose of drugs used to calculate the drug index

Drugs	Grams/Day
Cephalothin	8
Cefazolin	4
Ampicillin	6
Penicillin	2 million units
Oxacillin	8
Tobramycin	.22
Gentamycin	.22

TABLE III

Regression analysis of the effect of the Phase II drug control policy on the Drug Use Index of the injectable antibiotics over a 21-month period.

Drug	Drug Use Index			T	P
	B_0	$B_1X^{\dagger}$	DUI		
Combined Aminoglycoside & Cephalosporin	1.499	.002	.11%	.02	>.9
Cephalosporin	1.012	−.324	−32.0%	2.71	<.01*
Aminoglycoside	.494	.299	76.8%	3.31	<.01
Penicillins	.252	.012	4.8%	.27	>.9

* 1 tail T test

† X is a indicator function such that:
$X = 0$ when policy period was not in effect
$X = 1$ when policy period was in effect

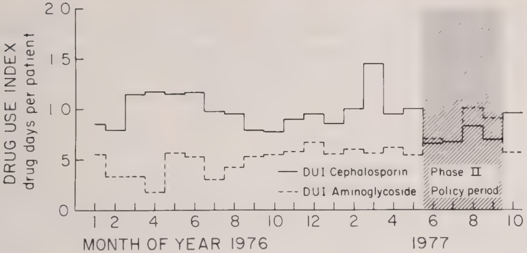

FIG. 1. Drug Use Index for the injectable cephalosporin and aminoglycoside antibiotics.

Discussion

The assumption that the prescribing habits of physicians could be influenced by supplying regular feedback has been substantiated. In this case, the policy Phase II resulted in a 32% reduction in the use of cephalosporin antibiotics. The estimated projected savings for the year would have been $50,000 had drug substitution not taken place. Directors of service have become aware of drug use in their departments and can check any unusual trends.

An unexpected and serious side effect of the policy was the undesirable increase in use of more toxic and equally costly antibiotics. It appears that pressure on the house staff to reduce the usage of the cephalosporins did not lead to a more careful evaluation of the appropriateness of antibiotic usage before initiating therapy. Rather, it resulted in a reflex selection of alternative agents.

Because of the marked increase of aminoglycoside use, the policy was discontinued in October, 1977 until a program could be developed which would include all injectable antibiotics. The DUI of both classes then returned to the prepolicy levels (Fig. 1).

Conclusion

The introduction of a policy to provide feedback to the medical staff resulted in decreased antibiotic use, yet it failed to improve prescribing behavior. The reduction in use of cephalosporins was totally offset by an increase of aminoglycoside prescription.

While this unanticipated consequence necessitated a temporary cessation of the program, it has provided information useful in planning Phase III. It appears essential that a monitoring and control system include all drugs in a particular class, in this case all antibiotics. Monitoring and control are insufficient without education of users, which should include attending staff as well as house staff.

It is useful to evaluate the program described above against the criteria stipulated by Brodie et al. Inadequate knowledge of the drug delivery system led to the erroneous assumption that cephalosporins could be controlled in isolation. Now that this is known, focus will move to model treatment criteria as part of an educational program so that efforts to regulate antibiotics will lead to better patient care and not to other unanticipated results.

Nevertheless, the Drug Use Index has proven to be a useful and simple method to monitor drug utilization. It will continue to be part of data collection and analysis technique used as efforts continue to control antibiotic utilization at Elmhurst.

It is useful to note in closing an editorial comment by Provost in *The American Journal of Hospital Pharmacy* which alerts us to the fact that efforts to regulate antibiotic utilization are necessary and worthwhile and that systems such as the one described above are of value: In the final analysis, however, the matter rests with the prescriber. And, in the long run, the rather alarming state of affairs in drug prescribing cannot be significantly improved in an overall sense until the basic education of those who will have authority to prescribe provides much more emphasis on pharmacology and therapeutics and more respect for the role of drugs in patient care (12).

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The Anesthetic Management of a Diabetic Patient Susceptible to Malignant Hyperpyrexia: A Case Report

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The syndrome of malignant hyperpyrexia (MH) was described by Guedel as long ago as 1951 (1) but it was not until 1962 that Denborough was able to characterize it as a familial disease (2). Subsequently, Britt and Kalow, Ryan, Harrison and others described the biochemical and electrophysiologic abnormalities that occur in the fully developed condition (3–6). That certain species of swine will develop the syndrome spontaneously, or can be challenged to do so, has greatly contributed to the knowledge and understanding of the condition (7, 8). Meanwhile the mortality as most recently reported has been reduced from 90% to 50%, largely by educating physicians to accept that such a condition exists and that it requires to be treated with all dispatch. The incidence, however, is quite small and it is variously quoted as lying between 1:100,000 for adults and 1:14,000 for children (3). Such figures inevitably come from hospital statistics and will vary according to the nature of the patient population, and to its geographic location. Since the overall mortality rate is still of the order of 50%, even in experienced hands the condition is potentially catastrophic (9).

Denborough in examining the history of an Australian family found that 10 fatalities had occurred in 39 administrations of anesthesia (2). This clearly pointed to a familial condition and currently MH is considered to be due to a single autosomal dominant of variable penetrance. The syndrome is divided into rigid and nonrigid classes by the clinical features observed, but the significance of such a division is open to question.

While hyperpyrexia during surgery can arise spontaneously (Cf. heat hyperpyrexia), the metabolic sequence of events in MH is known to be triggered by a wide variety of pharmacologic challenges, particularly succinylcholine (anectine), the halogenated hydrocarbons (halothane and ethrane) and "Amide" local anesthetics (lidocaine and mepivacaine), but all the commonly used anesthetic agents have been indicted to a greater or lesser extent on evidence of varying acceptability (10–13). Most hazardous is the combination of two potent triggers, notably succinylcholine and halothane, a very commonly used anesthetic sequence. Regional anesthesia, if appropriate, would appear to be prudent, but even spinal anesthesia with tetracaine (an ester) has been related to a clinical case (14). The common sequence of events in an established case are:

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1. Failure of relaxation to appear on induction of anesthesia or administration of a muscle relaxant.
2. Failure of the masseters to relax and consequent difficulty in laryngoscopy and intubation.
3. The administration of a further dose of relaxant or attempts to deepen anesthesia to overcome the difficulty.
4. Skeletal muscles becoming rigid and chest wall compliance decreasing.
5. Onset of tachycardia, often the first sign of the syndrome.
6. Marked venous oxygen desaturation.
7. Rapid rise in temperature, which has been known to exceed 112°F—such a rise can occur in less than 20 minutes.
8. The soda lime cannister overheats.
9. Severe tachypnea in the spontaneously breathing patient.
10. The tachyarrhythmia progressing to ventricular tachycardia, fibrillation and finally, stand-still occurs in systole, the myocardium being rock hard.

Gross acidosis, both metabolic and respiratory, develops simultaneously with severe hyperkalemia. In the later stages of treatment severe hypokalemia and disseminated intravascular coagulopathy often presage a fatal outcome. Myoglobinuria occurs if the patient survives for any length of time.

Less commonly, MH is heralded by an unexplained tachycardia developing during surgery, associated with a rapid and resistant rise in temperature, to be followed by the catastrophic events outlined above. This type of occurrence is not associated with marked muscle rigidity to the same extent although a preagonal rigor mortis may develop. It is to this form that the term "non-rigid" was first applied.

It is accepted that from the time of diagnosis, there exist about 20 minutes in which active aggressive cooling can abort the process and enable the patient to survive. The actual biochemical changes as suggested by Britt (4) are as follows:

1) Inability of sarcoplasmic reticulum to accumulate calcium.
2) This defect is exaggerated by halothane (at least in vitro) → reduced ATPase activity.
3) Raised mycoplasmic calcium stimulates several catabolic reactions.

Activation of
Phosphorylokinase

Activation of myosin ATPase
↓
Inhibition of tropinin
↓
Uncoupling of Mitochondria

Excessive production of heat and consumption of oxygen

This in turn leads to very high CO_2 levels, accumulation of lactate and actual destruction of the sarcolemma. Potassium, phosphate, and magnesium ions and myoglobin leak (or pour) out, while calcium enters the cell to perpetuate the biochemical derangement. In one case described by Ryan, where extracorporeal cooling was employed, it was calculated that the oxygen consumption had to be in excess of 2.3 liters per minute (normal = 0.2 liters per minute) to generate the heat removed by the exchanger (15).

It is clear that the management of such a situation is complex and that prevention, case detection and early recognition are the keys to successful management.

Case detection: The family anesthetic history is extremely important and should always be explored at the preoperative visit. One anesthetic death in a blood relative is suspicious, two or more would be highly suggestive of the existence of the atypical gene.

The surgical lesion is of importance; musculoskeletal deformities, herniae, strabismus, kypo-scoliosis, palatal deformities, osteo-facial abnormalities and excessively mobile joints are commonly associated with MH. Occasionally the subject may be excessively muscular and subject to frequent muscular cramps. An association with degenerative myopathies exists but is not clear cut. On the other hand, known affected families exist without such stigmata.

At one time it was hoped that measuring serum creatine phosphokinase (CPK) levels would provide a suitable screening test but this has not been substantiated. Some 45% of affected families do have CPK values that are persistently raised, but it is common to find many patients with raised values who are not at risk to malignant hyperpyrexia, and in 20% of affected families the CPK profile is normal (3, 6).

There is, however, a known association between raised CPK values, musculoskeletal deformities and malignant hyperpyrexia. Britt (16) suggests that to be meaningful the specimen for CPK determinations must be taken in the late afternoon after 5 days of abstinence from exercise, 24 hrs abstinence from alcohol, without a tourniquet and avoiding hemolysis. Such strictures preclude the use of this examination as a routine screen for case identification.

Muscle Biopsy: Microscopic changes have been well described by Britt, are clearly present, but not specifically diagnostic. Ergomyographic studies of the response to caffeine and halothane of a viable strip of muscle excised under general anesthesia are required for positive diagnosis, and are undertaken in only a few laboratories, to which the patient must be sent (9). Evidence thus accumulated has indicated that barbiturates, droperidol, narcotics, diazepam, pancuronium and nitrous oxide are the least provocative in such patients and may be used provided the correct precautions are taken in the operating room to control body temperature.

Recognition: Tachycardia, and a rising temperature are premonitory signs. Adequate monitoring is essential for the early detection of the onset of the syndrome. The rate of rise is important as well as the absolute value. Cyanosis and rigidity are ominous signs.

Treatment:

1. Terminate surgery.
2. Withdraw all anesthetic agents and ventilate with 100% oxygen.
3. If halothane has been used, change all lines from the anesthetic machine that have been in contact with volatile agents.

4. Institute vigorous surface and body cavity cooling; use cooled I.V. saline. Apply ice bags to groins and axillae.
5. Administer procaine, 1 mg/kg/min for 20 minutes.
6. Establish arterial line for biochemical analysis.
7. Administer sodium bicarbonate; up to 500 mEq/L may be required.
8. Pass Foley catheter; give lasix to reduce sodium load and mannitol to protect the renal tubules from myohemoglobin deposition.
9. If appropriate, give glucose and insulin to reduce serum potassium, being careful to avoid "overswing."
10. Do coagulogram.
11. Seek assistance from cardiac team for extracorporeal cooling.
12. Consider cold peritoneal dialysis if 11 is not available.
13. Once control has been achieved, as evidenced by a fall in temperature, and restoration of the acid base state to normal, transfer to the recovery room or ICU.
14. Avoid "overswing," especially with respect to temperature, serum potassium, serum calcium, alkalosis, and hypoglycemia.

Such patients are extremely unstable during transport and *must* be monitored continuously, even on short journeys.

The patient to be decribed, and her family, came to our attention when she brought her son, then aged five, for repair of a symptomless umbilical hernia. A first cousin had died in Michigan some years earlier as a result of malignant hyperpyrexia, developing during the course of repair of an inguinal hernia. The child's family was investigated and proved to contain a number of susceptible members, and the New York branch of the family were informed of this, but had taken no positive action. Our patient was advised that she and her son should submit to muscle biopsy to confirm the existence of the abnormality. By the kindness of Dr. Beverly Britt, this was carried out in the University of Toronto, and the results clearly indicated their susceptibility to the syndrome. "Medic-Alert" bracelets were issued and the family received counseling to assist them in living with this potential problem.

Surgery for the child was not advised. To complicate matters, the mother developed diabetes mellitus, requiring insulin for its control. Indeed, she appears to have a quite brittle type of diabetes and frequently had to vary her insulin dosage.

In January 1977 she sustained a prolapsed intervertebral disc which was managed conservatively in the first instance, but unsuccessfully, and surgery became indicated. Indeed, it would probably have been offered sooner if there had not been the added anesthetic risk of her susceptability to malignant hyperpyrexia. The reluctance is understandable, but such patients can be safely anesthetized provided that the existence of the syndrome is known and precautions taken.

Case Report

A 34-year-old female diabetic with known susceptability to MH (Fig. 1) suffering from severe backaches, was found on myelography to have a fragmented L4–5 intervertebral disk and scheduled

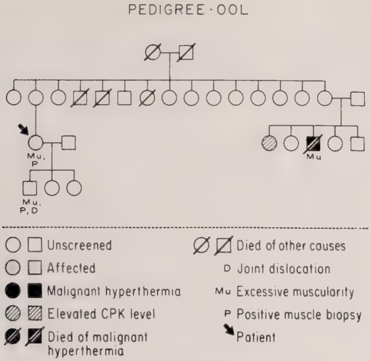


FIG. 1. Pedigree M.H. Susceptible Patient

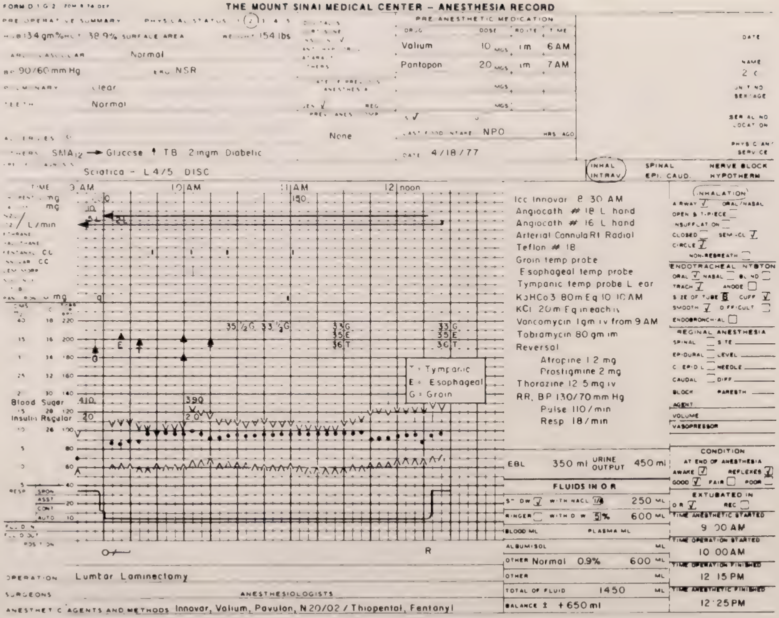
for lumbar laminectomy. History revealed two previous uneventful anesthetics for breast biopsy and ligation of varicose veins. She was receiving 15 units of NPH daily. Preoperatively she weighed 164 lb. The blood pressure was 90/60 and the pulse rate 84/minute and regular. EKG and chest x-ray were normal. Routine laboratory data were within normal limits with the exception of a blood sugar of 410 mg and a bilirubin of 1.2 mg.

Prior to surgery three special precautions were taken. Firstly, all vaporizers were removed from an anesthetic machine, which was then continuously purged with oxygen for 48 hours. Secondly, the cardiopulmonary bypass team was alerted. Thirdly, a special cart was arranged containing all available drugs which might be helpful in the event of a crisis and arrangements were made to insure an adequate supply of ice and intravenous solutions at 4°C.

Premedication consisted of diazepam 10 mg IM 2 hours preoperatively and Pantopon 20 mgs IM one hour preoperatively. In spite of this medication, she was extremely apprehensive and received 1 ml of Innovar on arrival in the holding area. A venous blood sugar at this time was 410 mg/% and 20 units of soluble insulin were administered. On transfer to the operating room, the patient was placed on a hypothermia blanket. In addition to routine monitoring aids, a size 18 Teflon catheter was placed in the R radial artery. The temperature was recorded from probes placed in the esophagus, external auditory meatus and left groin.

Induction of anesthesia was achieved with diazepam 10 mgs IV and thiopental, 100 mgs. IV. After ventilation with 100% oxygen and the administration of pancuronium, 9 mgs, IV, the trachea was intubated. Thereafter anesthesia and relaxation were maintained with nitrous oxide and oxygen, fentanyl and pancuronium. The patient was ventilated throughout. After one hour, a metabolic acidosis (Be − 8.3 meq/L) developed and this was corrected with 80 mEq of sodium bicarbonate. At that time the blood sugar was 390 mg % and serum potassium was 2.8 mEq/L. Regular insulin, 20 units IV, was administered and 40 mEq of potassium chloride were added to the intravenous infusion. Subsequent intraoperative laboratory data are listed in Table I. Throughout the procedure, temperature and vital signs remained stable (Fig. 2). At the conclusion of surgery neuromuscular blockade was reversed with atropine and prostigmine and spontaneous respiration easily reestablished. The patient responded rapidly and the endotracheal tube was removed in the operating room.

Following transfer to the recovery room, shivering occurred and was treated with IV thorazine. Her temperature remained normal throughout the day, but in the evening it rose to 101°F and a hypothermia blanket was utilized. Insulin coverage in the recovery room provoked a hypokalemic episode associated with a ventricular bigeminal rhythm. Normal sinus rhythm was restored after the administration of lidocaine (100 mg IV) and correction of the electrolytic imbalance.



THE MOUNT SINAI MEDICAL CENTER – ANESTHESIA RECORD

PRE OPERATIVE SUMMARY

PHYSICAL STATUS 1 [✓ 2] 3 4 5

Hb 13.4 gm% Hct 38.9% SURFACE AREA WEIGHT 154 lbs

CARDIOVASCULAR Normal

BP 90/60 mm Hg ECG NSR

PULMONARY Clear

TEETH Normal

PREV. ANES. None

OTHERS SMA₁₂ → Glucose ↑ TB 2 mgm Diabetic

Sciatica – L 4/5 DISC

PRE ANESTHETIC MEDICATION

DRUG	DOSE	ROUTE	TIME
Valium	10 MGS	im	6 AM
Pontopon	20 MGS	im	7 AM

LAST FOOD INTAKE NPO HRS AGO

DATE 4/18/77

[✓ INHAL INTRAV] SPINAL EPI. CAUD. NERVE BLOCK HYPOTHERM

Icc Innovar @ 30 AM
Angiocath # 18 L hand
Angiocath # 16 L hand
Arterial Cannula Rt Radial
Teflon # 18
Groin temp probe
Esophageal temp probe
Tympanic temp probe L ear
KaHCo3 80 mEq 10 10 AM
KCl 20 mEq in each iv
Vancomycin 1 gm iv from 9 AM
Tobramycin 80 gm im
Reversal
Atropine 1.2 mg
Prostigmine 2 mg
Thorazine 12.5 mg iv
RR, BP 130/70 mm Hg
Pulse 110/min
Resp 18/min

[✓ INHALATION]
AIRWAY ✓ ORAL/NASAL
OPEN & T-PIECE
INSUFFLATION
CLOSED SEMI-CL ✓
CIRCLE ✓
NON-REBREATH ☐

ENDOTRACHEAL INTUBATION
ORAL ✓ NASAL BLIND ☐
TRACH ✓ ANODE ☐
SIZE OF TUBE 8 CUFF ✓
SMOOTH ✓ DIFFICULT ☐
ENDOBRONCHIAL ☐

REGIONAL ANESTHESIA
SPINAL SITE
EPIDURAL LEVEL
C. EPIDL NEEDLE
CAUDAL DIFF
BLOCK PARESTH
AGENT
VOLUME
VASOPRESSOR

EBL 350 ml URINE OUTPUT 450 ml

FLUIDS IN O R
5% DW ✓ WITH NACL 1/4 250 ML
RINGER ☐ WITH D W 5% 600 ML
BLOOD ML PLASMA ML
ALBUMISOL ML
OTHER Normal 0.9% 600 ML
OTHER ML
TOTAL OF FLUID 1450 ML
BALANCE ± +650 ml

CONDITION AT END OF ANESTHESIA
AWAKE ✓ REFLEXES ✓
GOOD ✓ FAIR ☐ POOR

EXTUBATED IN
O R ✓ REC ☐

TIME ANESTHETIC STARTED 9 00 AM
TIME OPERATION STARTED 10 00 AM
TIME OPERATION FINISHED 12 15 PM
TIME ANESTHETIC FINISHED 12 25 PM

OPERATION Lumbar Laminectomy

SURGEONS

ANESTHESIOLOGISTS

ANESTHETIC AGENTS AND METHODS Innovar, Valium, Pavulon, N2O/O2 / Thiopental, Fentanyl

TIME
9 AM
10 AM
11 AM
12 noon
mg
mg
L/min
CC
CC
10
10
5
150
9
220
200
180
160
140
120
100
80
60
40
20
10
35½G 33½G
33 G
35 E
36 T
33 G
35 E
36 T
E
G
T = Tympanic
E = Esophageal
G = Groin
Blood Sugar
410
390
Insulin Regular
20
20
RESP
SPON
ASST
CONT
AUTO
R

FIG. 2. Anesthesia Record M.H. Susceptible Patient

TABLE I

Laboratory Data, Day of Surgery, MH susceptible patient

Na^+		K^+	Glucose	pH	PCO_2	PO_2	HCO_3	Saturation	OSM
meq/L		meq/L	mg %		Torr	Torr	meq/L	%	m/osms/L
8:55 a.m.	141	2.6	235	7.41	32.2	150.2	20.3	98.8	
10:00 a.m.	138	2.8	390	7.28	37.3	187.0	17.2	98.9	
10:35 a.m.	145.5	2.8	360	7.35	42.5	167.4	23	98.9	
11:15 a.m.	140.5	3.3	327	7.36	39.1	156	21.8	98.8	303
12:30 p.m.	143	4	260	7.24	48.4	97.5	20.1	94.9	305
14:25 p.m.				7.35	43	93.5	23.2	95.6	359

Postoperatively, she had a low grade fever of 100°F for five days, but recovery was otherwise uneventful. The serum CPK rose from 30 mu/ml to 1380 on the first postoperative day and gradually returned to normal, during the next seven days.

This case is presented for two reasons. Firstly, most of the published information has been concentrated in the anesthesia literature, while much of the experimental work stems from the economic importance of swine hyperpyrexia in the pork industry. Yet, rare as it is, knowledge of this condition requires to be more widely disseminated because of its increasing importance to the internist, the pediatrician, the specialist in sports medicine, as well as to the surgeon and anesthesiologist. Secondly, it has been noted by Denborough (17) that in MH susceptible patients there exists an increased glucose-induced insulin response. He further postulates that a membrane defect of calcium storage may be present in the B-cells of the pancreas. In this hypothesis may lie an explanation of why this patient's diabetes is difficult to control, and why she has a tendency to frequent episodes of hypoglycemia.

It is now clear that with a better understanding of this condition, greater ability to identify susceptible patients and adequate preparation, such patients can be safely negotiated through anesthesia and surgery.

Acknowledgment

The assistance of Drs. Seymour Gendelman, Stanley Mirsky and Ved Sachdev is gratefully acknowledged.

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Pancreatic Atrophy in the Canine: An Entity of Exocrine-Endocrine Dissociation

TIBOR SZABO, D.V.M., M.P.H., ADRIAN J. GREENSTEIN, M.D., STEPHEN A. GELLER, M.D., AND DAVID A. DREILING, M.D.

A study of exocrine and endocrine pancreatic function was carried out on two German Shepherd dogs, presenting with the clinical picture of pancreatic atrophy. They were two and three years old; each had developed anorexia, mild diarrhea, and weight loss of several months' duration. The differentiation from chronic pancreatitis was clearcut since the animals had little pain, diarrhea was not a major feature until a few months prior to admission, and there was no significant diabetes. The diagnosis was confirmed by unequivocal abnormalities in secretin testing, and gross and microscopic autopsy findings.

Materials and Methods

These two German Shepherd dogs were maintained over a period of approximately one year on a mixture of Purina and Alpo Dog Chow supplemented with Viokase to maintain normal absorption in the presence of impaired pancreatic function.

During the study period, they were followed closely clinically, maintained their weight, and remained in good health. Pancreatic function was monitored by systematic study of stool frequency, fat content, and careful examination for parasites. Routine blood counts and serum electrolytes were obtained.

Special Investigation

Exocrine pancreatic function was evaluated following insertion of a Thomas cannula into the duodenum. Cannulation of the major pancreatic was carried out in order to perform a standard secretin test using one unit of secretin intravenously as stimulus. Sequential volume, bicarbonate, and protein concentrations were determined in the pancreatic juice. Endocrine function was studied by routine glucose tolerance testing. In addition, blood secretin levels were obtained by a radioimmuno assay technique. We attempted to ascertain whether there was an increase in the circulating secretin levels in the blood resulting from pancreatic atrophy, to test the hypothesis that there was a feedback mechanism linking secretin release with bicarbonate production analagous to the Gastrin-Hydrochloric acid negative feedback mechanism established for the gastric antrum. This was carried out by study of the basal and stimulated circulating plasma secretin levels. To stimulate secretin release, 300 cc of hydrochloric acid at concentrations of 80, 120, and 160 mEq/L were

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given orally. Circulating secretin levels were carried out at the Bronx V.A. Hospital by Drs. Yalow and Strauss using a radioimmunoassay technique developed at the V.A. Hospital.

Clinical Findings

Case histories

Dog #1 was a German Shepherd dog, aged 22 months when first seen with a three month history of diarrhea. He had always been somewhat anorectic, and eaten poorly. He was referred to a veterinarian when he became depressed and was not as playful as usual. There was a recent increase in the number of his stools to approximately five times per day, the stools being of a yellow oatmeal consistency without blood or mucous. It was noted that Alpo made his diarrhea worse and he was put on Purina Chow and canned Kennel Ration. There was no family history of this disease and he responded to treatment with Viokase three times a day. Examination revealed him to be extremely thin but otherwise in relatively good health.

The five to six stools per day were somewhat pungent and had an acid pH of 5.3, well below the normal of 6.8 to 7.3. Examination of the stools for parasites was negative. There was a considerable amount of undigested starch and fat and numerous microorganisms of normal fecal flora including E. coli, aerobacteria and enterococci among others. He showed a normal red and white blood count and a normal serum protein of 6.3 with an albumin of 3. Serum diastase was somewhat below normal limits, 362 Somogyi units per milliliter against a normal of 420 to 560 but lipase was normal at .35 units per milliliter. The SGPT was increased 192 units per milliliter and the blood sugar was normal at 78 mg/100 ml. as was the BUN at 13 mgs/100 ml. Examination of the stool revealed a fecal fat of 76.8 grams every 24 hours vs a normal of 7 grams. Neutral fecal fat of 30.8 grams per 24 hours, and fecal fatty acids of 46 grams per 24 hours were also markedly increased.

Case history #2

The second animal gave a history similar to the first one, i.e. of diarrhea of fairly sudden onset with five to six bowel movements of a tannish stool daily. The stool was watery to semi-solid without any blood and was associated with mild borborigmi, flatulence, and coprophagia. Examination revealed an emaciated dog of quiet temperament and normal conjunctivae. Examination of the stools revealed a mean weight of 4,500 grams per 24 hours. Examination for parasites was negative and again the usual anaerobic and aerobic organisms were found in the stool. This dog did, however, exhibit a mild anemia with a red cell count of 3,800,000 and a hemoglobin of 9. The packed cell volume was 25. The white cell count was normal at 10,458. Examination of the blood proteins was normal. The total serum cholesterol was reduced to 60 mg% against a normal of 140, free cholesterol to 20 mg% against a normal of 28 and the cholesterol esters to 40 mg% against a normal of 423. No lipase was found and the SGPT was also slightly elevated at 156 sigma-Frankel units. The glucose was normal at 81 mg/100 ml. The fecal fat was 86 grams per 24 hours.

Results

Secretin Studies

The clinical impression of gross pancreatic destruction which was substantiated by serum and fecal fat studies, was confirmed by secretin testing. There was significant reduction in total volume, bicarbonate and total protein in each of the two dogs. The results are shown in Table I which reveal marked impairment in volume, bicarbonate, and total protein output when compared with normal control values. These findings confirmed the presence of almost total pancreatic atrophy in these two animals.

Glucose Tolerance Studies

Contrary to the studies on exocrine function, endocrine function as evaluated by glucose tolerance studies, indicated adequate insulin production. Both oral (using 1 gm/kg) and intravenous (using 0.5 gms/kg) glucose tolerance studies revealed glucose tolerance not significantly different from the normal (Fig. 1). Dog #1 did show a higher basal level than #2 with failure to return to below 100 mgs% until 140 minutes.

Clinicopathologic Correlation of Endocrine and Exocrine Function

Autopsy was carried out on these two dogs revealing in each instance normal intraabdominal viscera apart from the pancreas and peripancreatic tissues. Gross inspection of the region of the duodenum and pancreas showed, in each instance, grossly atrophic pancreatic tissue. In dog #1 the pancreatic tissue was so small in amount that the specimen taken for microscopy failed to reveal any definite acini, ductular tissue or islets. In view of the relatively normal glucose tolerance study it was concluded that this was due to a sampling error. The pancreas of Dog #2 demonstrated marked atrophy of exocrine acinar tissue and ductular structures, extensive replacement by fat, and relatively normal islets of Langerhans (Figure 2).

Secretin Levels

Secretin immunoassay to attempt to establish increased circulating secretin levels resulting from reduced bicarbonate levels failed to reveal any abnormality of secretin production. Basal levels and stimulated levels using concentrations of hydrochloric acid, at 80, 120, and 160 in mEq/L failed to demonstrate overt hypersecretinemia in either basal or stimulated state.

TABLE I

Secretin Study on 2 German Shepherd Dogs with Pancreatic Atrophy

	Dog #1	Dog #2	Normal Values
Volume*	0.10	0.08	2 ccs/kg
Bicarbonate**	49	74	90 Meq/l
Total Protein***	0.96	0.26	25 mgs

* ccs/kg/80 minutes

** Maximum mEq liter

*** Total protein output mgs/10 minutes

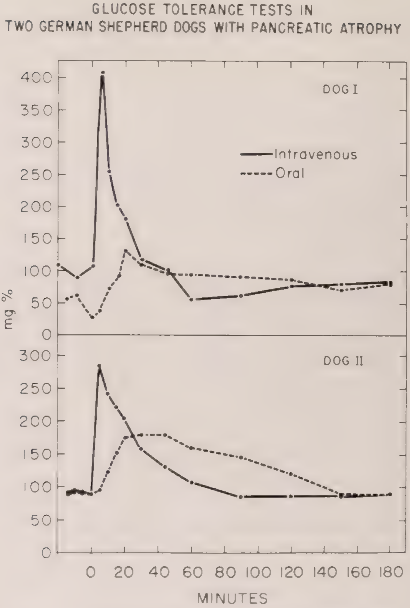
GLUCOSE TOLERANCE TESTS IN
TWO GERMAN SHEPHERD DOGS WITH PANCREATIC ATROPHY

FIG. 1. Glucose Tolerance Studies of Pancreatitis Dogs

Discussion

J. B. Stevens and R. L. Hardy (1) point out the importance of differentiating between juvenile atrophy, which usually occurs in the first two years of life and chronic pancreatitis. The prognosis in the former is much better than in the chronic inflammatory disease. The prolonged survival of these animals corroborate this impression, and it is probable that they could have been maintained indefinitely on an adequate low fat diet and Viokase. The difference in the clinical course is probably determined by the endocrine-exocrine dissociation found in this study, the determining factor being the diabetes which occurs in severe chronic pancreatitis but not in juvenile atrophy. Advanced chronic pancreatitis both in animals and man results in extensive fibrosis with destruction of the pancreatic islets of Langerhans, progressive reduction in the number of B cells, and ultimately impaired insulin release. In a study of Hill et al in 1971 (2) abnormal glucose tolerance tests were found in all of eight patients with degenerative pancreatic atrophy. On the other hand, Anderson

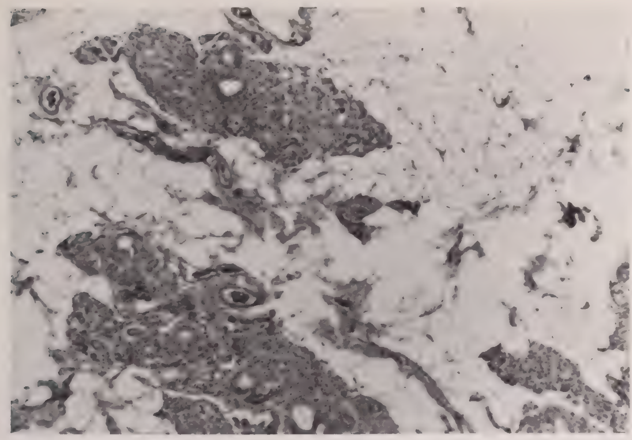

FIG. 2. Photomicrograph of pancreas from Dog #2 showing atrophy of exocrine pancreas with extensive fatty replacement. (Hematoxylin-eosin, original × 40).

and Low (3) have indicated that in juvenile atrophy overt diabetes mellitus has not been found.

Summary and Conclusions

This study confirmed the entity of pancreatic atrophy a clinicopathological picture found in German Shepherd dogs. It revealed an exocrine-endocrine dissociation with impaired exocrine function and normal endocrine hormone production. There was steatorrhea with increased fecal fat output in association with weight loss and debility. This was reversible and responded to the administration of Viokase and low fat diet.

Exocrine pancreatic function was markedly reduced as demonstrated by secretin testing. Endocrine function was excellent as proven by glucose tolerance tests. The relatively normal islets of Langerhans, and atrophy of acinar glandular tissue was confirmed by histopathological study.

Our study confirms previous findings in juvenile pancreatic atrophy, and emphasise the clinicopathologic entity of exocrine-endocrine dissociation in this disease. Every effort should be made to differentiate the more serious form of "true" chronic pancreatitis in which associated diabetes may lead to an earlier demise.

Acknowledgment

The authors wish to thank Herbert J. Van Kruiningen, D.V.M., Ph.D., of the University of Connecticut at Storrs, for referring these interesting cases to our Department.

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CLINICOPATHOLOGIC NOTES

STEPHEN A. GELLER, M.D. AND FIORENZO PARONETTO, M.D., COEDITORS

Adrenal Cortical Carcinoma with Cushing's Syndrome, Organic Psychosis, and Aphasia in a Seventy-One-Year-Old Woman*

Submitted by

ROBERT P. FRIEDLAND, M.D. AND WILLIAM O. WHETSELL, JR., M.D.

Case Report

A 71-year-old right-handed Caucasian female was admitted to the Psychiatric Service of The Mount Sinai Hospital because of progressive personality changes following a fall (without loss of consciousness) 6 weeks prior to admission. She was speaking "incoherently", mixing German and English. She was reported to have developed fearfulness and disorientation for a time as well as compulsive cleaning. Three days prior to admission she was unable to recognize friends and offered them gifts of silverware. There was a questionable history of poor memory for one year, definitely worse following her fall.

Six years previously an episode of "dysgraphia" was followed by residual difficulty in writing. She was hypertensive. There was no previous history of depression, elation or other mental dysfunction. Remaining medical history, as well as social and family history, and review of systems were not remarkable. She was not taking any medications.

On physical examination, temperature was 98.6F; pulse, 84; respirations, 16, and blood pressure, 150/108 mm Hg. She was found to be obese, disoriented as to time and place, negativistic, paranoid, hostile, and combative. She swung at examiners with arms and legs, and wandered off to other wards. She spoke with a mixture of German and English, and she was occasionally mute. The remaining physical and neurologic examinations were negative.

Laboratory studies revealed Na^+, 148 mEq/L; K^+, 2.0 mEq/L; Cl , 96mEq/L; BUN 17 mg%; glu, 101 mg%, PBI, 6.8 μg/DL; T_3 binding, 1.04 μg%; T_4, 4.4 μg%; complete blood count and platelet count were normal. EKG showed nonspecific ST changes. Chest x-ray showed kyphosis, with an enlarged heart. Skull x-ray demonstrated demineralization of the dorsum sella. Lumbosacral spine x-rays showed demineralization, scoliosis, and wedge-shaped deformities of vertebral bodies T-11, T-12, and L-1. Lumbar puncture revealed cerebrospinal fluid protein of 40 mg%, glu, 74 mg%, no cells. Cerebrospinal fluid VDRL was not reactive.

Left lower lobe pneumonia developing shortly after admission was treated with tetracycline. A fluctuating behavioral disturbance, with euphoria, restlessness, suspiciousness, perseveration, and disorientation was noted, and she was given Haldol 0.5 mg. four times a day. Potassium of 2.0–2.4 mEq/L was not noted until the 19th hospital day (HD) at which time oral KC1 and aldactone were administered. During the first 60 days of hospitalization, she became more manic and less paranoid with increasing evidence of speech disorder. She was noted to misname objects, and she had difficulty following commands. Serial speech, calculations, and reversals were poorly performed, and she was unable to rhyme or draw. The face-hand test was 4+. She was mildly ludic

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* Presented at Neurology Grand Rounds, The Mount Sinai Hospital, December 1976.

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with marked denial of illness. Episodes of head turning to the left with eye blinking and posturing of hands were observed, and a course of Dilantin 100 mg. three times a day was begun. When mild dyskinesias of the mouth, face, tongue, and upper extremities developed, Haldol dosage was decreased.

A right carotid arteriogram revealed a "vascularly staining neoplasm" in the region of the falx cerebri (midline) in the parietal lobe, the predominance of the neoplasm was on the left side (Fig. 1).

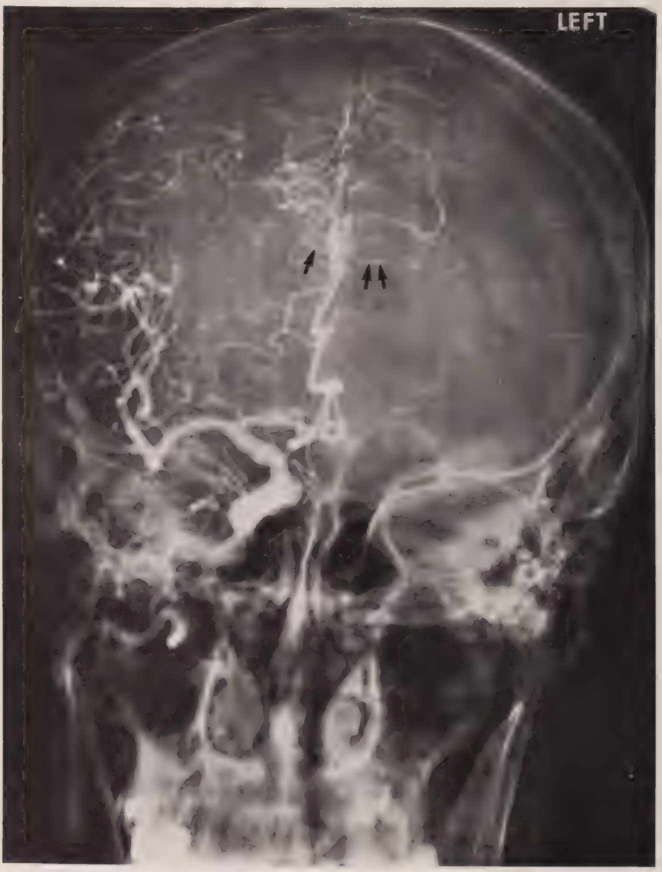

Fig. 1. Anteroposterior view of right carotid arteriogram demonstrating downward displacement of the left pericallosal cistern (double arrows), compared to the right, suggesting a parasagittal mass lesion.

Medical consultant noted Cushingoid facies, cervicodorsal fat pad, and trim, weak arms and legs with echymoses of knees and right ankle. Endocrine workup is summarized in Table I.

Laparotomy on the 74th HD disclosed a 14 cm, 145 gm, left adrenocortical carcinoma with invasion of renal vein. No gross tumor was left. The right adrenal was not visualized at surgery. She was treated with steroids pre- and postoperatively in decreasing doses. Three weeks postoperatively, she was noted to speak with singing voice, with clang associations, paraphasias, neologisms, and jargon. She was disoriented, incontinent, and had to be fed. She showed some signs of hypomania and spoke about herself in the third person. Neurologic diagnostic tests are summarized in Table 2.

She made a slow progressive recovery from the 100th HD to the 166th HD. She was discharged at that time to home with "minimal" organic mental syndrome (OMS) and speech deficits.

She did well following discharge, and plasma cortisol several months after surgery was: 8:00 a.m., 15.5 μg%; 4:00 p.m., 10.0 μg%.

She was admitted to the medical service of Mount Sinai Hospital 2-½ months after discharge with an OMS of 2 weeks duration. She was begun on ortho-paradichlorodiphenyldichloroethane (o,p'DDD) and Elipten (aminoglutethimide), both used as anti-adrenal agents. One day prior to admission, she became less responsive with 102° F fever.

Physical examination disclosed BP, 150/60; P, 100, and T, 102° F. There were Cushingoid facies,

TABLE I

Summary of Endocrine Tests (Normal Values in Parenthesis)

Serum cortisol (μg %)		
54th HD—9 am	29	(10–25)
87th HD—9 am	36.5	
89th HD—9 am	31	
97th HD—	20.0	
123rd HD—	18.0	
129th HD—	10	
Urinary free cortisol/24 hr. (μg/24 hrs)		
27th HD—	578	(20–100)
40th HD—	1040	
76th HD—	1263	
Urinary 17 KS/24 Hrs. (mg/24 hrs)		
27th HD—	21	(5–15)
76th HD—	10.7	
ACTH 56th HD (AM)—285 pg/ml (25–100)		
Plasma testosterone—21.5 ng% (NL)		
Plasma renin—low normal		

No change in plasma cortisol on both ACTH and vasopressin stimulation tests.

6 cm left adrenal mass noted on abdominal venogram, nephrotomogram and sonogram.

TABLE II

Summary of Neurologic Tests

EEG	4th HD,	13th HD—normal
	31st HD—	Left cerebral dysfunction with frontotemporal accentuation and slow bursts.
	40th HD—	diffuse cerebral dysfunction, right greater than left.
	75th HD—	diffuse cerebral dysfunction, symmetric
	130th HD—	diffuse cerebral dysfunction, worse temporally.
	152nd HD—	normal

Brain Scans on 3rd, 18th, 45th, and 94th HD's all showed a midline parietal area of increased uptake, without change.

Right Carotid Angiogram on 59th HD showed a large, midline parietal vascular mass in the region of the falx (see figure #1).

buffalo hump, excess facial hair and abdominal striae. She was disoriented, alternately stuporous and agitated. Distal muscle wasting was noted. General physical examination was normal. No neurologic examination was recorded.

Laboratory investigation disclosed: glu, 123 mg%; CO_2, 36 mg%; Cl, 90 mEq/L; Na, 140 mEq/L; K, 19 mEq/L; BUN, 10 mg%; Ca, 8.3 mg%; P, 1.7 mg%; Hgb, 11.2 g%; WBC, 9,000 mm^3; normal differential; ESR, 100 mm/hr, and platelets, 399,000 mm^3. Serum cortisol ranged from 30 to 61 μg%. Urinary free cortisol/24 hours was 1170 μg. Urinary 17 ks/24 hours was 9.40 mg. T4 RIA ranged from 1.1-1.6 μg%. T3 binding was 0.99 μg%. EKG showed nonspecific ST changes. Chest x-ray disclosed an enlarged heart. Abdominal ultrasonogram was normal. EEG revealed some degree of diffuse cerebral dysfunction. Brain scan was unchanged from previous studies.

OMS, disorientation, perseveration with occasional euphoria continued with evidence of hypercortisolism despite o,p'DDD and Elipten and treatment with thyroid hormone. After 1-½ months, her condition worsened with agitation and screaming. Multiple fevers with parotitis and proteus, E. coli, and Klebsiella urinary tract infections developed. She had progressively higher fevers to 106° F despite antibiotic treatment and died on the fifty-fourth hospital day.

Neurologist's Discussion

Robert P. Friedland, M.D.

In summary, this is the case of an elderly hypertensive woman suffering from an organic paranoid psychosis with manic features and Cushing's syndrome (CS) secondary to adrenocortical carcinoma. A fluent aphasia developed and a large midline parietal intracranial mass was identified. Resection of tumor was followed by improvement, but 5-½ months postoperatively, she relapsed and died with metastatic disease, 10 months after presentation.

The outstanding question in this case is that of the origin of her complex symptomatology. Were her behavioral changes produced by her endocrine disturbance, her brain tumor, or by a combination of the two? A question of greater simplicity, as will be discussed later, is the nature of the brain tumor itself. The former of these problems will be discussed in some detail, as this case is a valuable example of the complex interrelationships between steroid hormones and brain function.

She was first admitted to the Psychiatric Service with incoherent speech, personality changes and memory loss. It is well known that organic brain disease should be suspected in all patients over 30 or 40 with the onset of severe psychiatric symptomatology, but without previous history of such difficulty. She also had definite organic features early in the course of her illness, with disorientation for time and inability to recognize her friends. It is of interest to note that she was recorded as having been an "obsessive cleaner" for her entire life. This was exaggerated to a pathological degree following the onset of her disease. It is a common observation that personality features characteristic of a patient continue to characterize them after the development of an OMS.

Severe disorders of affect may be seen in many varieties of organic disease of the brain. Keschner et al (1) reported in 1938 a 46% incidence of affect disturbance in a series of 530 brain tumors. Most marked were hyperirritability, depression, anxiety and euphoria. This study failed to reveal any relationship between tumor location and affect changes in cases with supratentorial tumors, although most authors today would say that such phenomena would be more likely with frontal or temporal lesions, especially if both hemispheres are involved. Similar behavioral changes can be seen in dementias of any etiology. Her affect disturbances prompted the administration of Haldol, and shortly thereafter oral-facial and extremity dyskinesias developed. Extrapyramidal signs have been reported rarely in CS, but commonly with Haldol treatment. The movements disappeared after Haldol withdrawal. Perhaps her head turning and posturing were also Haldol induced dyskinesias.

We have little information on her 6-year history of dysgraphia. I assume that it was due to a central process. Writer's cramp or local pathology of the right hand should not have been described simply as dysgraphia. We know that she had a large bilateral parietal brain tumor, more on the left side. It is conceivable that the only symptomatic evidence of a mild aphasia was in her writing, that is, aphasic patients can have more difficulty writing than speaking. The reverse is not true; normal writing is not really compatible with aphasia. In the hospital, however, definite aphasic symptomatology developed as her paranoid features diminished. Perhaps this is because the examiners were able to establish better contact with her.

The disturbance of language function observed in this patient was the product both of the left cerebral lesion and the diffuse metabolic encephalopathy. Each of these can produce abnormal speech, as can functional psychoses. The differential diagnosis of disturbed language may present a difficult problem at times (2, 3). Our patient's tendency to mix two languages can be seen in patients with an OMS, in jargon aphasics or in psychotics. The phenomenon of clang associations, as observed here, represents a form of loosening of associations where patients jump from one idea to another in speech on the basis of the phonemic similarity of words, but without regard to meaning. This, as well as singing speech, may be seen in jargon aphasia or with psychosis. Demented individuals without focal disease of the traditional language areas may demonstrate severe poverty of speech with diminished vocabulary. Although they may have difficulty naming objects, neologisms or paraphasias are not commonly seen. They may also demonstrate echolalia. The speech of psychotics generally does not reflect inadequate vocabulary, but bizarre utilization of words revealing an underlying thought disorder may be seen (2). Neologisms and paraphasias may be seen in psychosis, but true word salad, resembling jargon, is exceedingly uncommon. Critchley (2) has referred to an increased use of the first person pronoun "I" in schizophrenic speech. Our patient was noted to use the third syntactical person in referring to herself (e.g., "She is not feeling so good today; She would like to go out"). This may be seen as a symbolic representation of denial of illness (4).

Jargon aphasia or anosognosic aphasia is a form of fluent speech disturbance accompanied by denial of illness. Ludic behavior, euphoria, paranoid ideation, and disorientation may frequently accompany jargon. Our patient had all of these. Weinstein (5) has suggested that the dysfunction involved in jargon aphasia extends beyond cortical language areas to involve limbic-reticular connections. This additional level of dysfunction may have been an effect of her Cushing's syndrome. I will have more to say about this later.

On admission potassium was 2.0 mEq/L, but this was not noted until the 19th HD. At that time, medical consult revealed definite evidence of CS, with obesity, thin, weak extremities, moon facies, buffalo hump and ecchymoses. Laboratory investigation revealed marked elevation of serum cortisol and urinary cortisol. CS is produced by excessive pituitary ACTH production in 60% of cases. There is, commonly, a basophilic or less commonly, a chromophobe pituitary adenoma in these patients (6). Many patients with bilateral adrenal hyperplasia have no pituitary tumor and may have excessive hypothalamic production of corticotrophin releasing factor (CRF). Ectopic ACTH may be produced by systemic carcinomas, most commonly lung, producing CS. Adrenocortical carcinoma and adenoma may also cause the disease. Diminished potassium is seen more frequently with the severe steroid excess produced by adrenal carcinoma than in that associated with pituitary adenomas. The failure of suppression with dexamethasone demonstrated by our patient is also characteristic of adrenal carcinoma, as is her advanced age.

Adrenocortical carcinoma is a rare disease, accounting for about 10% of CS (6). This tumor produces steroids inefficiently, therefore, discovery of such tumors, because of the production of CS, is usually delayed, and the tumors are not resectable in three-fourths of the cases. It is of interest that in the early days of adrenalectomy for CS, before the importance of steroid coverage was realized, patients with metastatic disease did better than those whose carcinomas or adenomas were completely removed, because patients with metastases did not become Addisonian due to continued production of steroids by residual tumor. These tumors disseminate via vein invasion and, incidentally, cases with tumor tails extending up and into the right heart have been described.

The only finding that does not seem to fit in this case is the elevated ACTH. ACTH levels in functioning adrenocortical carcinoma should not be obtainable due to suppression of hypothalamic CRF production. The adrenal carcinoma itself may have been producing ACTH. There is only one report of an ACTH-producing adrenal carcinoma, that in an 11-year-old child (7). In that situation, one would expect the opposite adrenal to be hyperplastic. Our patient's right adrenal was never visualized. A patient with a functioning adrenocortical carcinoma producing cortisol should have an atrophic opposite adrenal. It will be interesting to see what the appearance of her right adrenal was at autopsy.

There are several factors in this case which may have been responsible for her behavioral disturbances. First, she had severe hypokalemia on both hospitalizations. Electrolyte abnormalities are notorious for their association with mental changes (8). Hyperaldosteronism with water retention is just one example and this may be seen in Cushing's syndrome, but was not noted in this particular case. Severe hypokalemia may be seen in hypokalemic periodic paralysis or in primary aldosteroidism without any evidence of CNS malfunction. Katzman (9) has demonstrated that profound changes in serum potassium are accompanied by only slight changes in brain extracellular potassium in animals. However, hypokalemia may cause a reversible myopathy with patchy coagulation necrosis and elevated CPK (9). Perhaps this was responsible for her elevated CPK on the first admission. (Steroids also commonly produce myopathy and myopathy is commonly seen in CS, but elevation of CPK is not seen in these cases.)

She also had a large bilaterally situated intracranial space occupying lesion. Such tumors can produce behavioral phenomena such as we have seen here. However, she improved markedly following laparotomy and may have been asymptomatic before her fall. In addition, her postoperative improvement and subsequent deterioration appeared to be in direct correlation with her serum cortisol. Her intercranial mass lesion could not be felt to be solely responsible for these symptoms.

OMS may develop in patients with metastatic carcinoma via several mechanisms, aside from direct metastases to the brain. These include an increased tendency to infection with bacteria and fungi and the development of a disseminated intravascular coagulopathy. These patients may also develop progressive multifocal leukoencephalopathy, nonbacterial thrombotic (marantic) endocarditis and encephalopathy as a remote effect of the carcinoma. We see no evidence for these entities in this case. The antiadrenal therapy (O,p'DDD and Elipten) which she received for her tumor may have contributed to the development of her abnormal behavior. O,p'DDD (6) is an insectiside derivative of DDT which inhibits adrenal glucose 6-phosphate dehydrogenese, effectively diminishing tumor growth and steroid production in many cases. Up to ⅓ of the cases may show no response. 40% of the patients may develop lethargy, sommolence, dizziness and vertigo on this drug. Elipten (6) is an anticonvulsant, also acting on adrenal enzymes to diminish steroid production. It can produce lethargy, ataxia and depression of thyroid function due to a block of iodine organification. This was most likely responsible for the hypothyroidism seen in this case. Her hypothyroidism may have contributed to her deterioration during her second hospitalization.

I feel that her Cushing's syndrome was responsible for her behavioral changes. Several possible mechanisms can be offered in regard to the genesis of behavioral changes with CS. CS patients have an increased susceptibility to infection. There is no evidence for a CNS infection here. Mental alterations may develop in these patients as a result of sodium retention with congestive heart failure or as a complication of severe hypertension or uncontrolled diabetes mellitus. No evidence for these disturbances was noted. Soffer et al (10) has reported hydrocephalus in 5 of 8 brains of CS patients. Cortical atrophy was also seen in 3 women all below 47 years of age. In addition, steroid treatment may be associated with dilated ventricles as seen on CT scans in patients with rheumatoid arthritis. The angiogram of our patient disclosed normal ventricles and her improvement to near normal following adrenal surgery is not consistent with cortical atrophy. Also, we note that she had ecchymoses of her lower extremities. This is due to increased skin fragility in these patients, with no bleeding tendency. She had no evidence of intracranial bleeding. My last and favored choice is a direct effect of hypercortisolism on the brain. Mental changes are reported in 50–60% of CS patients (11)(12) Most commonly seen are depression, insomnia, memory loss, anxiety, increased libido and irritability. Up to 20% of the patients have severe mental changes with delusions, hallucinations, depression and delirium. One study reported suicide attempts in 10% of CS patients (12).

EEG's in CS patients with mental changes may be entirely normal but commonly reveal diffuse slowing, occasionally with sharp activity (11). This patient's EEG findings did not correlate with either neurological findings or steroid levels. Euphoria, as demonstrated by this patient, may be seen with manic psychosis in CS. It is of interest to note that elevation of mood is not commonly seen in CS while it is very frequently observed in steroid induced psychosis and mild mood elevation is very common in patients on steroids. Organic changes are more common in CS then in steriod psychosis. Mental changes in patients receiving steroid medication are not uncommon and range from euphoria to depression, occasionally with organic features (13)(14) These changes are more common with higher doses but are not strictly dose related. The obvious correlation of steroid induced mental changes to those seen in CS was recognized early and has helped to establish hypercortisolism as the important factor in their production.

Much important information has recently been elucidated concerning steroid-brain interactions. A review of these developments would be valuable here in consideration of the possible pathogenetic mechanisms involved in our patient's behavioral disturbances. Steroids act in the cell nucleus and stimulate or modulate RNA synthesis, thereby regulating enzymatic activity. Various steroid effects on enzymatic systems which have been documented in certain areas of the CNS in animal models include increased activity of phenylethanolamine N-methyl transferase (the enzyme converting norepinepherine to epinephrine), increased glutamine synthetase, increased production of serotonin from tryptophan, and diminished activity of monoamine oxidase (15)(16). Cortisol has been demonstrated to increase norepinephrine reuptake. Gamma-amino butyric acid transaminase and glutamate decarboxylase are diminished following adrenalectomy. Electrophysiological changes induced by steroids include diminished synaptic delay (6), slowed axonal conduction (17) and diminished REM sleep (15). Adrenalectomy has been shown to increase the ease of induction of electroconvulsive seizures. In addition, steroids are intimately related to sensory processes (15)(17). An impaired ability to detect and recognize sensory signals has been seen in CS.

It is of interest to observe that, contrary to what one would expect, steroid uptake is greatest in the hippocampus and *not* in the hypothalamus (15). Other evidence has been developed demonstrating a close relationship between the limbic system and the pituitary-adrenal axis (18)(19)(20). Hippocampal lesions may increase while hippocampal stimulation may inhibit ACTH release and steroids may increase excitability of the hippocampus. It is of interest to observe that brain tumor patients given steroids show improvement earliest in the behavioral manifestations of their disease, that is, in disturbances of consciousness, disorientation or hemi-inattention (21). Evidence of primary motor or sensory deficit improves more slowly in these patients. Perhaps part of their improvement is related to steroid effects on limbic system and is not due to relief of edema alone.

A number of observations have been reported concerning the effect of steroids and ACTH on behavior (15). ACTH increases the maintenance (delays extinction) of a conditional avoidance response (this is true even in adrenalectomized animals). On the other hand steroids increase the extinction of a

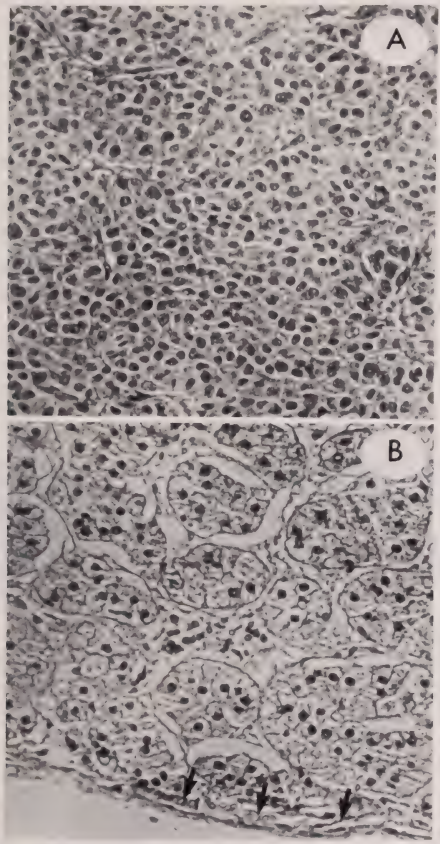

FIG. 2. A. Portion of the highly-cellular adrenal cortical tumor composed of cords and nests of cells separated by a delicate fibrovascular stroma. (Hematoxylin and eosin, 250×). B. Portion of right adrenal cordex demonstrating normal configuration of the thin, small-cell layer of the zona glomerulosa (arrows) just beneath the gland's capsule. The broader zona fasciculata, comprising most of the tissue visible here, is made up of moderately large, clear cells arranged in glandular nests separated by thin fibrous trabeculae. (Hematoxylin and eosin, 250×).

conditioned-avoidance response. In other words, ACTH may act to aid the retention of learned responses, promoting remembering, to maintain an adequate state of arousal during early reaction to stress. Steroids may serve to aid the elimination of nonreinforced behavior assisting the essential process of forgetting. Thus steroids play a vital role in the modulation of behavior.

Our patient's periods of greatest disability were associated with the greatest degree of hypercortisolism. Her disorientation, memory loss and mood changes at those times may have been related to steroid effects on limbic system. Also her jargon aphasia may have reflected limbic system disturbance in the presence of a lesion on the left side of the brain.

It must be kept in mind that steroids are secreted in response to stress. This may be represented as fear, rage, apprehension, or anxiety. Psychological stress, even hope or disappointment may very effectively trigger the pituitary-adrenal system and the limbic system may be intimately involved in this triggering (15). So we see how this patient during her hypercortisol period may have been suffering from the effect of an overactive system designed to enable the organism to adapt adequately to stress. Her problem, of course, is that she was that way all the time. She may have had alterations in brain enzymes, neurotransmitters, sensory processing and limbic system activity with abnormal patterns of sleep.

I would like to discuss the possible role her brain tumor played in her course as well as the nature of the lesion itself. All of her behavioral changes, except aphasia, can be accounted for in terms of steroid effects on the brain. CS patients without brain tumors commonly have changes identical to hers. Her organic features may have been more marked, but she was 71 years old. The

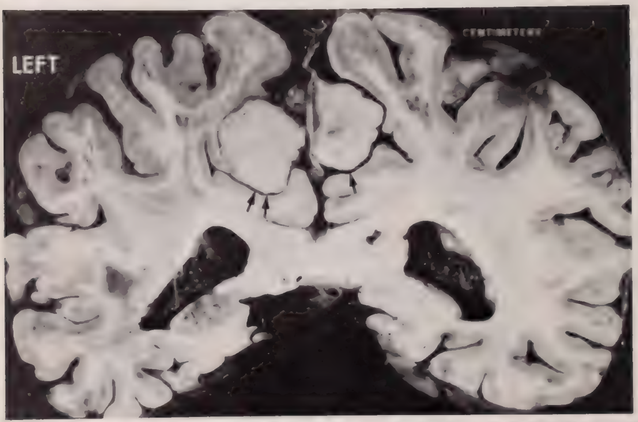

FIG. 3 Posteroanterior view (standard view) of coronal section through the fixed brain at the level of the bodies of the lateral ventricles (parietal lobes). Note large bilateral parasagittal neoplasm impinging on the medial aspects of either cerebral hemisphere.

brain tumor was a large midline mass, in the area of the falx cerebri, extending into both hemispheres. Review of her brain scans shows no change in the lesion over an 8 ½ month period, suggesting a very slow growing lesion which had been there for a long time. Tumors in this location, with its size, would be expected to produce paraparesis with urinary symptoms, aphasia and probably an organic mental syndrome. We know that she had few symptoms preceeding her fall before her first admission and made an excellent, though delayed, recovery following adrenal surgery. These factors point to a lesion of great chronicity and possibly one lacking local invasiveness.

Her brain lesion may have been there for some time with only minimal symptoms (possibly dysgraphia). The steroid-induced metabolic encephalopathy may have aggravated the effect of her brain tumor and interfered with mechanisms of recovery of function. It is a common observation that symptoms resulting from structural disease of the brain, such as tumors or the plaques of multiple sclerosis may be exacerbated by metabolic factors. When diffuse cerebral dysfunction of metabolic origin was added to focal left parietal dysfunction previously successful compensatory mechanisms may have no longer been effective. These postulates would be most plausible if her brain tumor was benign and had been there for a long time, as I believe was actually the case.

Intracerebral metastases of adrenocortical carcinoma must be considered, but is very unlikely in this case. This cancer is very malignant, but rarely goes to brain, going virulently to liver, lungs, lymphatics and bone. Four studies of this tumor, including 243 cases, report 8 brain metastases, only two verified histologically (22)(23)(24)(25). It is interesting to observe that in a series of 62 pediatric cases of adrenocortical carcinoma, 4 brain lesions were recorded, 2 astrocytomas, 1 hypoplasia of left posterior cerebral cortex and 1 arachnoid cyst of the posterior fossa (26). Cases have also been reported of association of the disease with choroid plexus cysts and papillomas and aqueductal stenosis (27)(28). It would have been interesting in this case to have measured CSF steroids to see if her brain lesion was actively secreting them (28).

Schoenberg (29) has recently studied 135 patients with primary tumors of the brain and unrelated tumors elsewhere and found that 41% of these patients had meningiomas. This may reflect the chronicity of that tumor and this chronicity is one of the reasons why I feel we are dealing with a meningioma in this case.

10–15% of all brain tumors are meningiomas. These lesions are among the few primary brain tumors more common in women and their greatest incidence is in the 6th and 7th decade. Jayk (30) reports a 40% incidence of elevated CSF protein with meningiomas but the incidence must be higher with tumors of this size. Falx meningiomas comprise 3–7% of all these tumors and have a brain scan and angiographic appearance similar to our case. Of course, these are the slowest growing of all brain tumors and very large lesions may exist with little deficit. Surrounding cerebral edema may be minimal and they do not invade brain tissue. Our patient had an endogenous source of steroids which may have played a role in the reduction of tumor related edema.

In conclusion, I would like to postulate that Dr. Whetsell may have selected this case to commemorate the legacy of Harvey Cushing, who made vital contributions in both of these disease entities. In 1932 Cushing (31), at the age of 63, described a case of pituitary basophilism, ascribing what had been called the "poly-glandular syndrome" or "diabetes of bearded women" to a pituitary tumor for the first time. Actually, one of Cushing's cases was found in a mental hospital with depression, irritability, and poor memory. In 1922, (32), he introduced the term meningioma, replacing "dural epithelioma" and was the first correctly to localize the cell of origin of this tumor.

I believe that pathological examination of this case will reveal that the immediate cause of death was bilateral bronchopneumonia. General autopsy will reveal adrenal cortical carcinoma metastatic to liver, lung and bone. Examination of the brain will disclose a large parietal falx meningioma, extending into both hemispheres, left greater than right. In addition, if skeletal muscle is examined, selective atrophy of type II fibers may be evident. The presence in this extraordinary case of elevated ACTH suggests that pathological examination of the right adrenal will reveal a normal or hyperplastic cortex.

Pathologist's Discussion

William O. Whetsell, Jr., M.D.

Operative Findings

The resected specimen was a large, yellow-tan, encapsulated tumor measuring 14 × 7.5 × 4 cm, in greatest dimension and weighing 145 grams. Cut surfaces displayed a variegated pattern with scattered areas of hemorrhage and necrosis. The neoplasm invaded the wall and protruded into the lumen of a large vein emerging from the mass. A portion of preserved, partially-encapsulated adrenal gland could be identified attached to the tumor mass.

Microscopic examination (Fig. 2A) demonstrated highly cellular neoplasm composed of cords and nests of cells with abundant acidophilic cytoplasm: the cellular aggregates were separated by a delicate fibrovascular stroma. Individual cells of the neoplasm showed some variation in size: nuclei appeared hyperchromatic, some with two or more nuclei. Mitotic figures were frequent. The wall of a large vein was invaded by tumor cells. Sections through the junction of adrenal gland and tumor showed transformation from normal adrenal tissue to neoplastic tissue.

Surgical Diagnosis

1. Adrenal cortical carcinoma: tumor composed of nests and cords of moderately pleomorphic cells with hyperchromatic nuclei and frequent mitotic figures.
2. Normal adrenal gland.

Autopsy Findings

A large tumor mass measuring 20 × 13 cm. was found in the left retroperitoneal space. The mass, which surrounded the left kidney, was composed of soft, yellow tissue. Microscopic appearance of the large neoplastic mass was identical to that of the neoplasm removed at surgery seven months before the patient's death.

The tumor invaded the left kidney, and sites of metastasis were observed in both lungs, the spleen, the liver, and the bone marrow. The right adrenal gland, however, bore no evidence of neoplasm or adrenal cortical atrophy (Fig. 2B).

Elsewhere in the endocrine system, the pituitary gland showed prominent Crooke's hyalin change in the anterior lobe consistent with cortisol excess (endogenous or exogenous), but there was no other pituitary abnormality; the gland was of normal size and shape.

Examination of the brain revealed a well-encapsulated, bilateral parasagittal meningioma arising from either surface of the middle third of the falx cerebri. The left lobe of the tumor measured 2.5 cm in its greatest diameter; the right lobe, 1.5 cm in greatest diameter. Both portions of the tumor had produced significant compression of the medial aspects of the parietal lobes and the cingulate gyri (Fig. 3). No other abnormalities were noted in the brain or spinal cord.

This case focuses attention on several aspects of the so-called "incidental meningioma" in combination with an unusual manifestation of a primary adrenal cortical carcinoma. An association between occurrence of meningiomas and primary malignancies elsewhere in the body, though to our knowledge never reported with adrenal cortical carcinoma, seems to be well-recognized for a number of other malignancies (29). A point to be emphasized, here, is that in the presence of central nervous system symptoms in an individual with a primary malignancy outside the nervous system, the possibility of a meningioma should be considered as well as the possibility of a metastatic lesion (29).

The incidence of intracranial neoplasm, particularly meningioma, as a primary but often-unrecognized cause of psychiatric symptoms has also been documented in a number of reports over the last several decades. Patton and Sheppard (33) point out that, in particular, meningiomas are frequently asymptomatic and may appear in psychiatric patients with greater frequency only because there may be a more thorough postmortem brain examination in these patients than in "nonmental" patients. However, it should be emphasized that meningiomas have been considered an important cause for psychiatric symptoms frequently with no specific manifestations other than progressive dementia and reduction of adaptive capacity (34).

The effects of the primary adrenal cortical carcinoma in this patient, however, are also a major consideration in determining the pathogenesis of the neuropsychiatric disturbances which presented clinically. There is no evidence of brain metastasis in this case. I mention that in passing, only because of the extreme rarity of such an event; there are only two cases of metastasis of adrenal cortical carcinoma to brain documented in the world literature (22)(23).

The systemic effects of the tumor in this patient, supported by the elevated levels of cortisol, produced a full-blown Cushing's syndrome. Though primary adrenal carcinoma is rarely a cause of Cushing's syndrome, psychiatric symptoms in patients with Cushings syndrome of whatever cause are not rare (11). Gabrillove (11) states that psychiatric symptoms including paranoia, confusion, disorientation, marked emotional lability, or significant memory defects, can occur in about half of the patient's with Cushing's syndrome. Specific neurologic symptoms may occur in perhaps one-third of CS patients, and these most frequently consist of headaches, paresthesias of lower extremities, seizure disorders, or occasionally peripheral neuropathy.

We are, therefore, faced with two separate pathological entities in an individual with neurological symptoms which might be attributed to either entity. Our dilemma is to attempt to differentiate the pathological etiology of her symptoms, if that is possible. The evidence of hyper-cortisolism, the development of the physical signs of Cushing's syndrome, and the presence of the Crooke's hyalin change in an otherwise-normal pituitary, all confirm the effects of the steroid-producing neoplasm in this patient. Her postoperative improvement and subsequent deterioration, appearing in direct correlation with her serum cortisol levels, add further evidence of the effects of this neoplasm. The remitting and exacerbating course in the presence of the clearly demonstrable parasagittal meningioma indicates that the effects of the adrenal carcinoma were the overriding basis for the clinical course in this patient. The meningioma, though it produced a large primary intracranial mass, was probably not the cause of the neurologic symptoms.

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RADIOLOGIC NOTES*

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D., COEDITORS

Case No. 396

Submitted by

ALBERT MILLER, M.D.**

A 63-year-old woman was referred for evaluation of an abnormal chest x-ray. She was active and free of symptoms; physical examination revealed only an inconsistent wheeze bilaterally. She had smoked 25 cigarettes per day until 18 months previously when she noted hemoptysis and underwent left-lower-lobectomy for a moderately differentiated adenocarcinoma with extensive squamous metaplasia. Hilar lymph nodes were negative. X-rays of the chest including tomograms in the frontal projection (Fig. 1) showed several thin-walled, cystic lesions in the right middle and lower lobes and evidence of a left lower lobectomy. X-rays of the chest taken 6 months (Fig. 2) and one month (Fig. 3) before the Figure 1 x-ray, revealed smaller cysts and a solid nodule at the site of the present lesions.

Mammography and roentgenographic examination of the GI tract were normal. Intravenous pyelography showed arteriosclerotic scarring. Radionuclear scans of the skeleton, liver and brain were negative. On fiberoptic bronchoscopy, the biopsy forceps appear to enter the thin-walled cavities in the right mid-lobe and the right lower-lower lobes. Tissue removed from both sides revealed adenocarcinoma and brush biopsy was positive for malignant cells. The patient was placed on chemotherapeutic program of Adriamycin, Cytoxin, Methotrexate and CCNU every 3 weeks. Shrinkage of the lesion was noted at 8 weeks and complete resolution at 4 months after the start of the treatment (Fig. 4). This has been maintained until the present time, 8 months after the beginning of therapy.

Discussion

Cavitation of pulmonary metastases is uncommon. It was observed in 16 (4%) of 398 consecutive patients, compared with 9% of 176 patients with primary lung tumors investigated by Dodd and Boyle (1). In 1965, LeMay and Piro (2) added 9 cases for a total of 72 in the world literature to that date.

In most cases of cavitary pulmonary metastasis, diagnosis is not difficult, as

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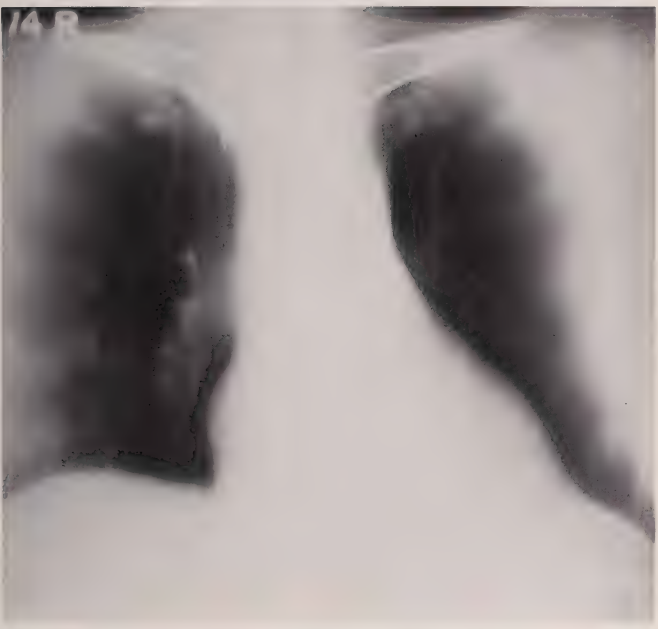

FIG. 1. Tomographic section in the frontal view reveals a number of well demarcated, sharp, thin-walled lesions in the right-mid-lung field. There is no evidence of hilar adenopathy. The remainder of the right lung appears normal. There is evidence of a previous left lower lobectomy.

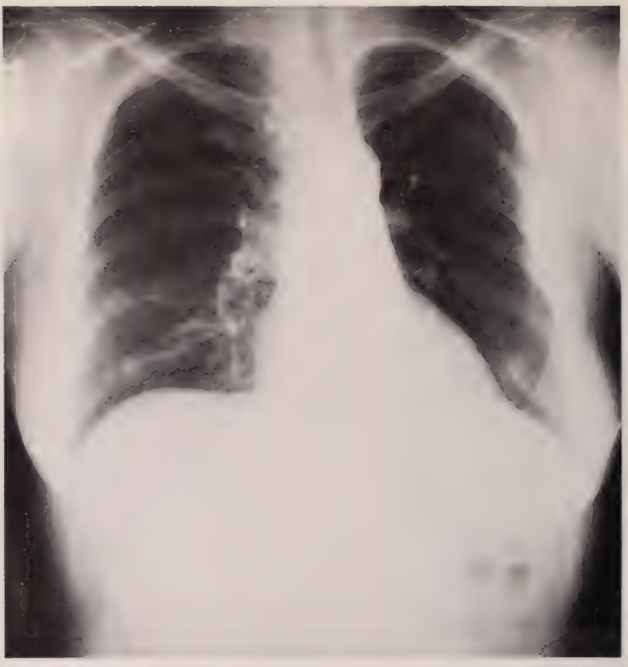

FIG. 2. Chest x-ray in the frontal projection taken 6 months before Fig. 1 reveals numerous solid nodules and small cysts in the right-mid-lung field. The remainder of both lungs appear normal. There is evidence of a previous left-lower-lobectomy.

noncavitary nodules and masses are generally present (2,3) and the cavitary lesions show thick, irregular or nodular walls. When all the lesions are thin walled, as in the present case, the correct diagnosis is suggested by the history of preceding or coexistent malignancy.

Most cavitary metastases are squamous (69% in one series (1)) with primary sites in the head and neck in males and in the genital tract in females. The remainder are adenocarcinomas, generally of the lower bowel or pancreas (1,2) or sarcomas (4). A primary in the lung is quite unusual. (5) Dodd and Boyle (1) cite 4 cases of a bronchogenic primary seen after the analysis of their series, in which no primary was in the lung. It is of interest that the histology in the present case showed an overlap of squamous and glandular features.

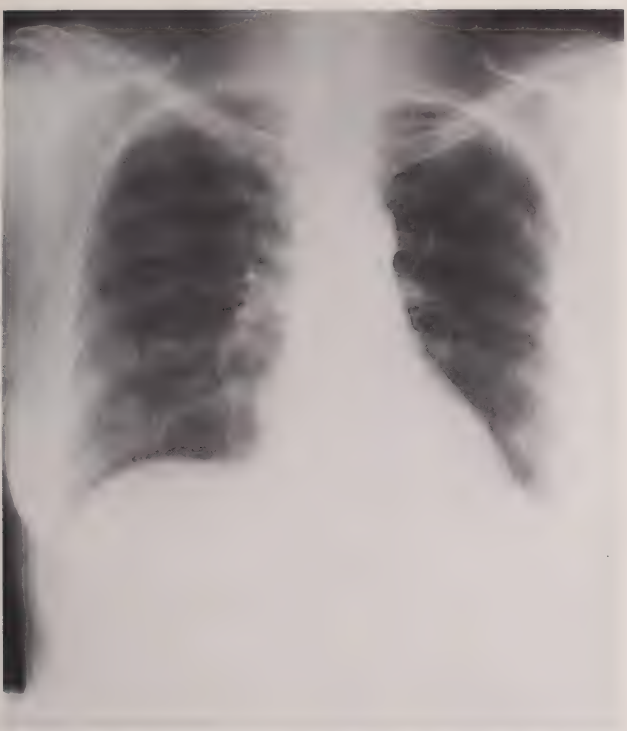

Fig. 3. A film taken one month before Fig. 1 reveals a solid nodule in the lower-lung-field on the right side as well as at least one cystic lesion in the right-mid-lung field.

The present patient demonstrates several other roentgenographic findings typical of metastatic disease presenting as pneumatoceles. Solid lesions may become cystic (as in this case) or cystic lesions solid. The pneumatoceles generally increase in size but the thickness of their walls remains constant, suggesting that cells are shed internally. (1) Small multiple lesions may present initially as cysts, making excessive tumor growth relative to blood supply an unlikely pathogenic mechanism for excavation.

Lung cysts are defined as air containing lesions greater than 1 cm in diameter with a smooth or crenated wall of minimal thickness (1,6). Although metastatic

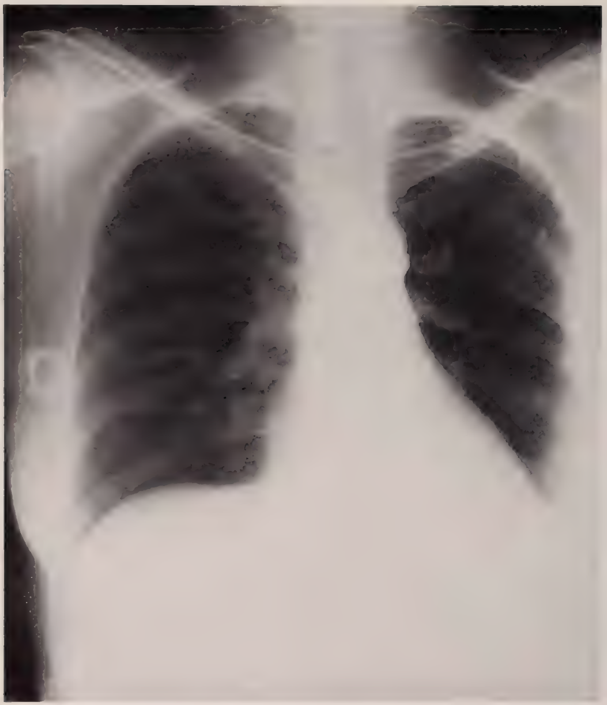

FIG. 4. Examination of the chest in the frontal view reveals complete disappearance of the nodules and pneumatoceles in the right lung. This x-ray was performed 4 months after onset of chemotherapy.

malignancy must be included in the differential diagnosis of acquired cysts, more common etiologies in an otherwise normal lung are postinfectious (staphylococcal or streptococcal pneumonia, tuberculosis, fungal disease or lung abscess) or posttraumatic. Unusual causes include varicella pneumonia (7), pulmonary xanthomatosis (8) and rheumatoid disease (9).

Case Report: PNEUMATOCELES REPRESENTING METASTATIC LESIONS FROM A CONTRALATERAL BRONCHOGENIC CARCINOMA.

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Case No. 397

Submitted by

GEORGE HERMANN, M.D.* AND KENNETH SUEN, M.D.†

A 37-year-old woman was first seen suffering from intermittent pain in the right knee. Radiologic examination of the right knee disclosed an expanding cystic lesion involving the upper end of the right tibia (Fig. 1). The radiologic appearance suggested giant cell tumor of bone. The patient was admitted to the orthopedic service for surgical excision. She had been in general good health previously. Her former history included oophorectomy for ovarian cyst and appendectomy, both at age 29. She had had two children. The family history was noncontributory. At operation, curettage and bone package were performed and the right leg was put in a cast.

The curetted specimen consisted of numerous fragments, the largest of which measured 2 × 1 × 0.5 cm. Portions of the curetted fragments were composed of bone spicules. The remainder of the specimen was soft, tannish red, friable tissue. Histologically it proved to be plasma cell myeloma (Fig. 2). In some areas the cells were quite poorly differentiated, with binucleate and trinucleate bizarre cells among them. For the most part, however, the malignant cells were identifiable as plasma cells. After the histologic diagnosis of plasma cell myeloma was established, repeated examinations, including serum immuoelectrophoresis and urine study for Bence-Jones proteins were made but the findings were always negative. Radiological survey of the skeleton was unremarkable except for the above described lesion in the right tibia. Radiation therapy was applied locally. 3000 R was given during a period of three weeks to complete the treatment. Since the time of the operation, the patient has

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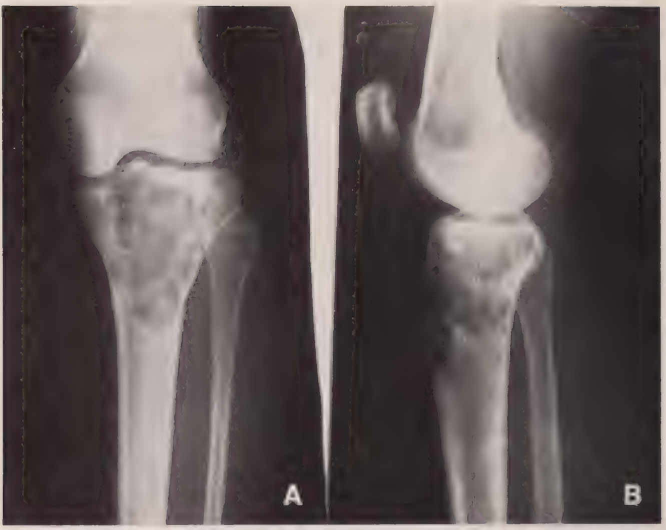

FIG. 1a&b. Antero-posterior and lateral view of the right knee. There is a radiolucent multicystic pattern involving the proximal end of the tibia. The cortex is thin but preserved. The articular cartilage is intact.

returned to the hospital several times with different complaints unrelated to the myeloma lesion. Each time, complete laboratory and radiological examinations failed to reveal any additional abnormality. The previously curetted tibia showed no progression of the disease (Figs. 3a and 3b) and the last skeletal, performed fifteen years after the initial curettage, showed no evidence of dissemination.

Discussion

Myeloma (plasma cell myeloma or plasmacytoma) is a fairly common malignant disease which usually occurs from the sixth decade onwards (1) with increasing frequency. Sometimes the disease is first manifested by a solitary lesion, but within a few months to one to two years, it disseminates (2).

The reason for presenting this case is that the solitary lesion was located in an unusually site and radiologically presented as giant cell tumors of bone in a young woman. The lesion was locally treated and a fifteen year followup failed to reveal any evidence of local recurrence or disseminated bone lesions.

Radiologically, two types of solitary osseous myeloma can be differentiated. One is a purely destructive form that commonly involves the axial skeleton. The second form has a multicystic appearance. It is rare, allows a relative benign course (3) and usually involves the pelvis, occasionally the long bones.

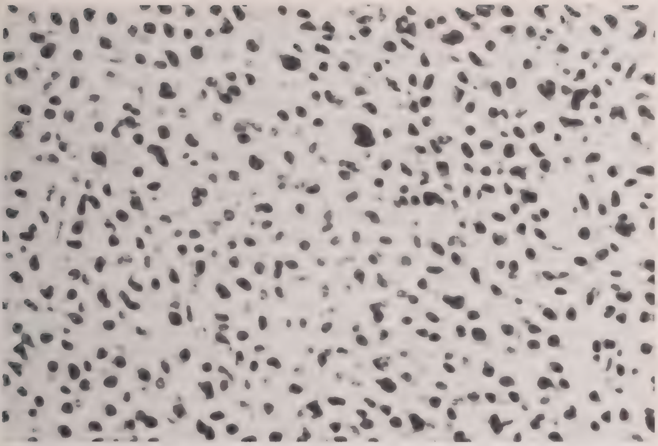

FIG. 2. Photomicrograph of the curetted tissue showing sheets of malignant cells, most of which are identifiable as plasma cells. Occasional bizarre multinucleated Cells are seen (H & E, × 400).

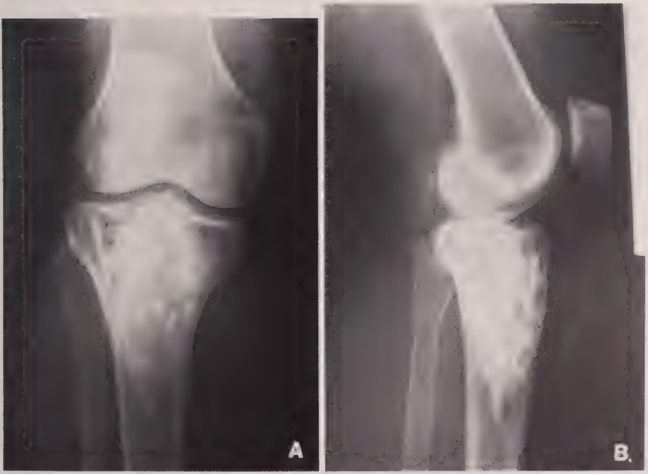

FIG. 3a and Fig. 3b. Antero-posterior and lateral view of the right knee—15 years after curettage and bone package. The proximal end of the right tibia shows increased calcified density. No evidence of extension of the lesion. The cortex of the tibia as well as the articular cartilage is intact.

It can show an expanding pattern if it is localized to the end of the long bone and closely resembles giant cell tumor. Histologically it must be differentiated from plasma cell granuloma which is actually a reactive hyperplasia of the bone marrow (4). This lesion radiographically can imitate plasmacytoma, but the presence of the inflammatory cells such as lymphocytes, histiocytes among the abundant plasma cells, evidence of vascularization and sometimes fibrosis, favor an inflammatory process.

The fact that patients with solitary myeloma have a much better prognosis than with disseminated myeloma has been well documented (5). Griffith (6) reviewed 78 cases of solitary myeloma most of which disseminated within five years and only one survived and was followed for 10 years without progression. Seventy-five per cent of the cases were localized in the axial skeleton and only one involved the tibia. More recently, Meyer and Shulz (7) reported 12 cases of solitary myeloma of bone. Two of them had survived 5 years without dissemination following treatment of the primary lesion. The longest survival, that of 30 years, has been described by Pankovich and Griem (8), although several recurrences occurred since the initial diagnosis.

Case Report: SOLITARY PLASMACYTOMA MIMICKING GIANT CELL TUMOR OF THE BONE—LONG-TERM FOLLOWUP.

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Case No. 398

Submitted by

ARTHUR SICULAR, M.D.* AND A. LAWRENCE OSSIAS, M.D.**

This 27-year-old man was admitted with right-lower-quadrant pains of 24-hour duration. The patient had been in previously excellent health. Epigastric pain extending into the right-lower-quadrant were present for 24 hours before admission. There was slight elevation of the white count with a shift to the left. Sedimentation rate and other laboratory functions were normal. Plain film of the abdomen revealed no mass lesion or abnormal calcifications in the right-lower-quadrant (Fig. 1). Because of an ill-defined fullness in the right-lower-quadrant without rebound, a barium enema was performed. During the barium enema a filling defect was first encountered in the distal portion of the ascending colon. A lobulated mass was seen outlined with barium (Fig. 2). As the barium proceeded towards the proximal portion of the ascending colon, the lobulated mass was pushed further proximally by the barium column and a coilspring appearance was seen (Fig. 3).

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When maximally distended, the proximal portion of the ascending colon revealed a lobulated mass on the medial aspect in the region of the ileocecal valve (Fig. 4).

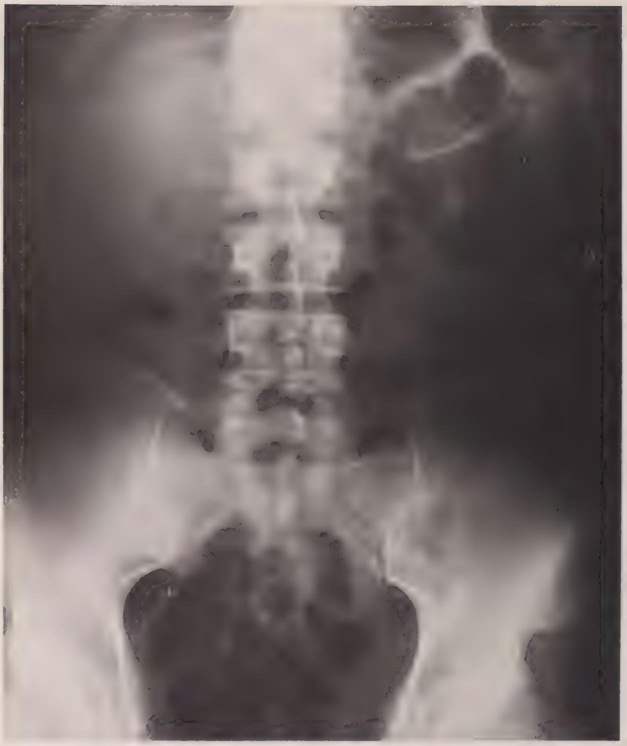
In spite of two separate attempts to further reduce the intussusception, no barium was noted in the region of the terminal ileum. A postevacuation film (Fig. 5) revealed a sharply demarcated, somewhat lobulated intraluminal defect in the region of the cecum with no barium having refluxed into the terminal ileum.

Because of the findings on barium enema, the patient underwent bowel preparation and a right hemi-colectomy and ileectomy was performed. Enlarged lymph nodes were seen and the lesion proved to be a lymphocytic lymphoma of the ileocecal valve. The enlarged lymph nodes were all inflammatory in nature without evidence of neoplastic involvement. An ileotransverse colostomy was performed and the patient had an uneventful postoperative recovery.

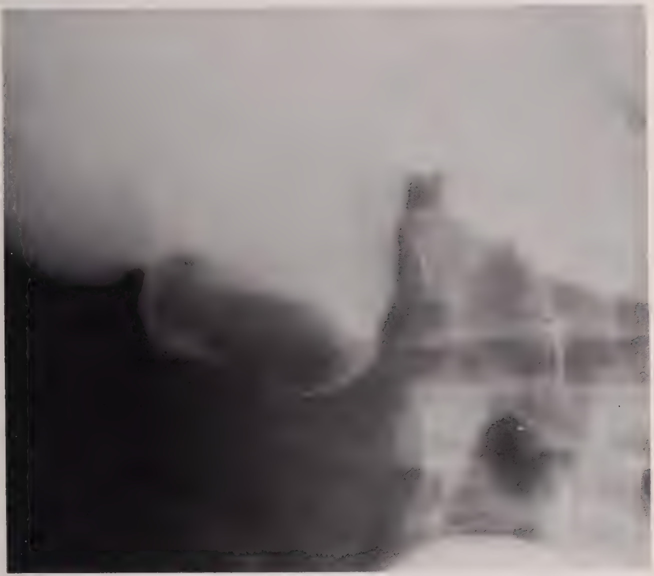
Discussion

Intussusception is most commonly encountered in the pediatric age and especially in the first 6 months of life. In only approximately 5% of these young patients is there a pre-existing lesion that can be demonstrated at the head of the intussusception. The most common causes are Meckel's diverticulum. Benign polyps and enlarged nonneoplastic lymphoid hypertrophy in the terminal ileum and cecum are often the cause in the pediatric age group. In the adult population, one of the leading causes for intussusception of the cecum into the distal colon is lymphoma. Mestell, in a review of intestinal lymphosarcoma in children, found 39% with intussusception (1). The incidence was approximately 20% in the adult age group which was presented in a paper by Speese (2). Twenty to thirty per cent incidence of intussusception was noted in small bowel lymphomas in other papers (3, 4).

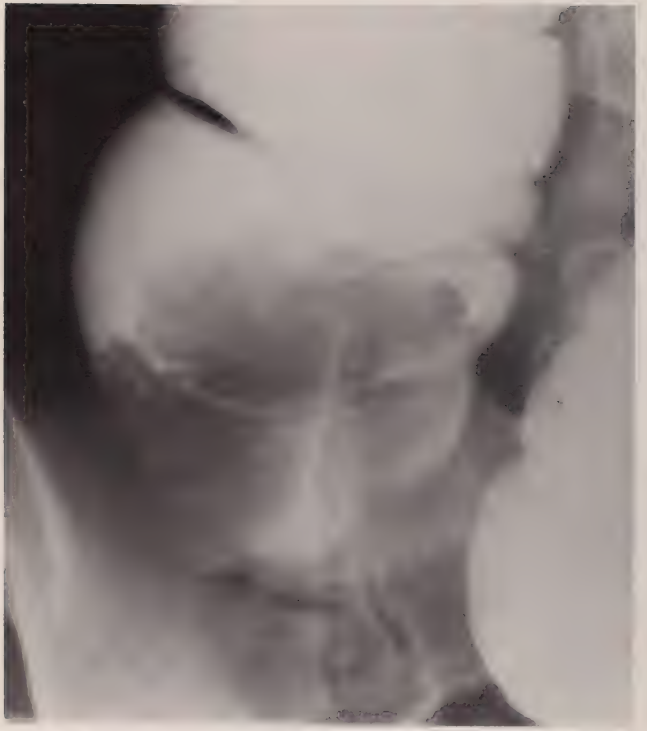
Either non-Hodgkins or Hodgkins lymphoma can produce a similar lesion which may lead to the intussusception. If the disease is localized to the cecum, the prognosis is good. Radiologically, besides the intussusception, one has to demonstrate a polypoid mass as in the case presented. In the differential diagnosis, one has to entertain the possibility of carcinoma of the cecum or a



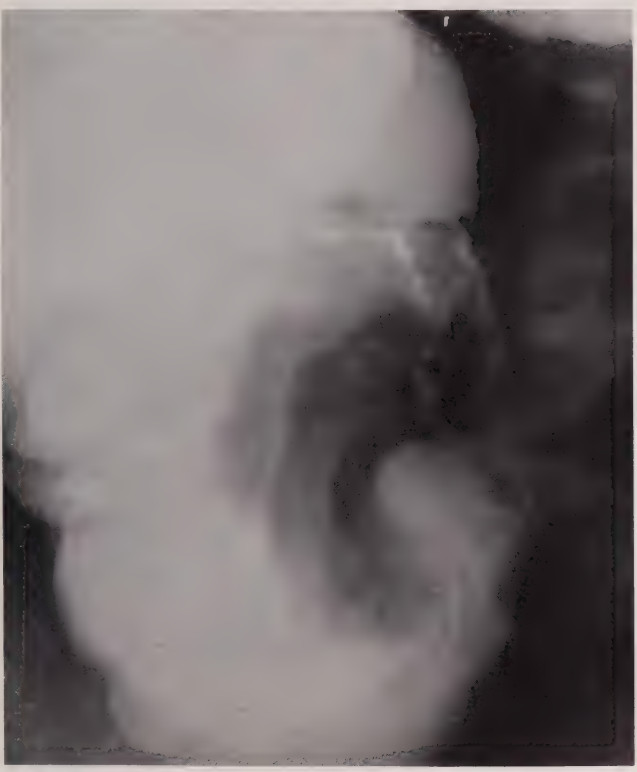
Case 398, Fig. 1. Examination of the abdomen in the supine projection reveals a minimal amount of small bowel dilatation in the right side of the pelvis and the left-upper-quadrant. No abnormal soft tissue masses are seen and there are no abnormal calcifications.



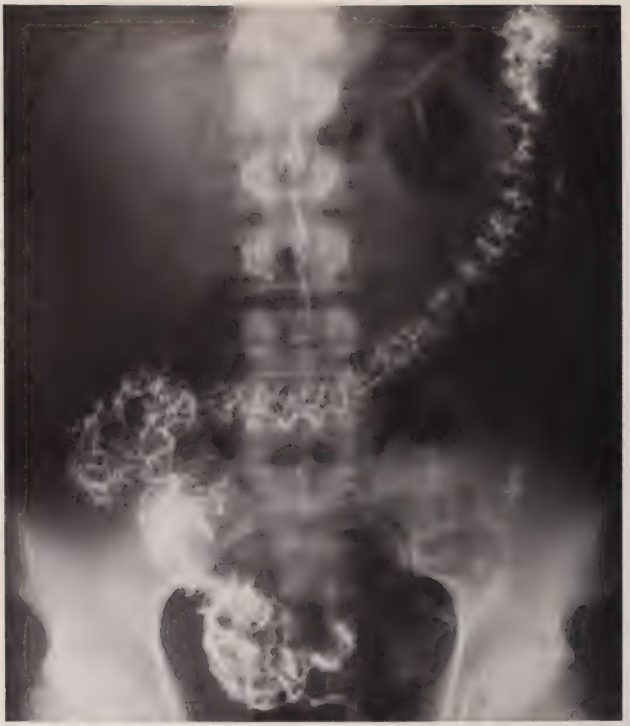
Case 398, Fig. 2. Barium enema with a spot film of the distal ascending colon reveals barium delineating a lobulated intraluminal mass with barium outlining most of the periphery of the mass itself.



Case 398, Fig. 3. During the course of the barium enema the polypoid mass is now displaced more proximally within the ascending colon. Barium demonstrates a "coil-spring" appearance with the lobulated mass clearly noted.



Case 398, Fig. 4. When maximally distended at the end of the barium enema, the cecum is well outlined. On the medial aspect of the cecum, there is the lobulated mass which is in the expected position of the ileocecal valve. No barium was seen refluxing into the terminal ileum.



Case 398, Fig. 5. Post-evacuation film reveals a well demarcated, lobulated intraluminal lesion in the ascending colon. No barium was seen in the terminal ileum.

lipoma of the large bowel. In children, intussuscepting Meckel's diverticulum or polyp is the most frequent cause for the right sided intussusception.

Case Report: Intussuscepting lymphoma of the cecum.

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NEUROLOGIC-NEUROSURGICAL NOTES

ALLAN E. RUBENSTEIN, M.D. AND MARTIN H. SAVITZ, M.D., COEDITORS

Pseudotumor Cerebri: Occurrence during the Third Trimester of Pregnancy

Submitted by

JAMES T. CAROSCIO, M.D. AND MONTE PELLMAR, M.D.

Pseudotumor cerebri, or benign intracranial hypertension, is a syndrome characterized by increased intracranial pressure without focal neurologic deficits or cerebrospinal fluid abnormalities.

Hormonal disturbances have been implicated in the etiology of pseudotumor cerebri. The syndrome may be seen in Addison's disease (1), and during steroid withdrawal (2); the vast majority of patients diagnosed as having this condition are young women with menstrual irregularities (3).

The occurrence of this syndrome during pregnancy has also suggested a hormonal role in its etiology (3, 4, 5).

We wish to report a case of pseudotumor cerebri with onset in the last trimester of pregnancy, a situation not previously described in the literature.

Case Report

A 20-year-old gravida 2 P1001 woman in her eighth month of pregnancy was admitted to The Mount Sinai Hospital for evaluation of bitemporal headaches of one month's duration.

The headaches increased in severity in the two weeks prior to admission. They were unrelieved by acetaminophen and were exacerbated by bending or straining. One week prior to admission she experienced total loss of vision in both eyes which lasted for 10 seconds. Since that time she described her vision as cloudy. She had a past history of irregular menses. Her only medication throughout the pregnancy was a standard multivitamin tablet which she took once a day.

On examination, the patient was an obese pregnant female in no distress. Blood pressure was 120/70. There was no pedal edema. On neurological examination, positive findings were confined to the eyes. Visual acuity was 20/25 OU corrected. There was bilateral papilledema with a hemorrhage adjacent to the disc at 12 o'clock in the right eye. On visual field testing, the blind spots were bilaterally enlarged.

Admission laboratory data: Hemoglobin was 10 mg%; white blood cell count and differential were normal; serum iron was 40 mg% (normal 59 to 200 mg%); total iron binding capacity 334 (normal 200 to 400 mg%). SMA-6, SMA-12, urinalysis and serum protein electrophoresis were all normal. T-3 binding ratio was 1.25 (normal .85 to 1.15); T-4 by radioimmuno assay was 5.8 mg% (normal 4.5 to 13.5 mg%); 17 Ketosteroids were 15.7 mg/24 hours (normal 5 to 15 mg/24 hours); free cortisol was 47.3 ug/24 hours (normal 10 to 100 ug/24 hours); serum estriol was 9.8 mg/ml.

On lumbar puncture, opening pressure was 480 mm H_2O. The fluid was clear and colorless with

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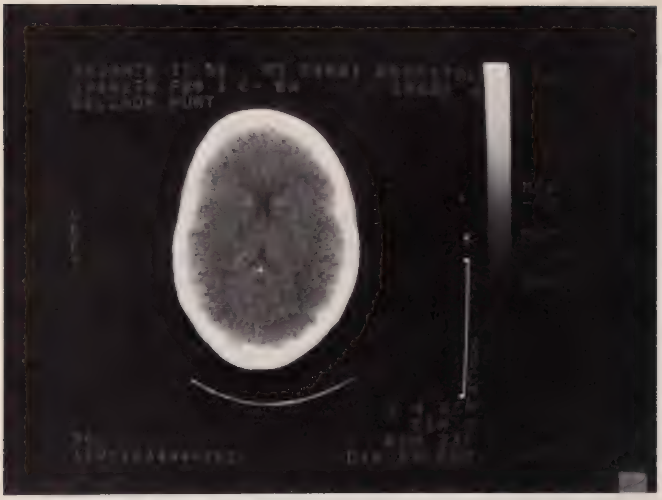

FIG. 1. CAT scan of patient showing normal ventricular size and configuration, and normal brain parenchyma.

a protein of 29 mg% and a glucose of 51 mg%. There were 4 white blood cells and 1 red blood cell per mm^3 of cerebrospinal fluid. Skull x-rays and computerized axial tomography (see figure 1) were normal.

A diagnosis of pseudotumor cerebri was made and the patient was treated with bedrest and a total of 3 additional spinal taps where the opening pressure ranged from 360 mm H_2O to 260 mm H_2O. An average of 12 cc of cerebrospinal fluid was removed at each tap, and closing pressure was in the normal range. Her headaches were resolved with this treatment. She was followed closely with frequent checks of visual acuity which remained unchanged, and frequent fundoscopic exams which showed persistent bilateral papilledema. Two months after admission the patient was vaginally delivered of a healthy 7 lb. 3-1/2 oz. baby girl.

One week after delivery there was blurring of the nasal margin of the right disc, and the blind spots were of normal size. Fundoscopic examination done four months after delivery was entirely normal.

Discussion

Several reports of pseudotumor cerebri occurring in the first and second trimester of pregnancy have previously appeared. Weisberg reported two cases of pseudotumor with onset in the first trimester (4). Paterson et al (3) reported two cases with onset in the second trimester. Greer reported eight cases of pseudotumor cerebri in pregnant women whose period of gestation at the time of onset of symptoms ranged from two to five months (5). Donaldson states that benign intracranial hypertension commonly begins in the the third, fourth or fifth months of gestation (6).

Greer suggested that a state of relative adrenal insufficiency occurs in the second trimester of pregnancy which predisposes to pseudotumor cerebri (5). His hypothesis relied heavily on studies which demonstrated a decrease in the excretion of glucocorticoids in the fourth through six months of gestation after an initial rise during the first trimester (7). More recent studies on steroid metabolism during pregnancy have shown that plasma cortisol levels rise progressively and that there is either no change or only a slight increase in the excretion of cortisol metabolites. Indeed, there is now general agreement that plasma levels of free or unbound cortisol, which is the biologically active steroid, actually increase during pregnancy (8). These studies support observations that patients with Addison's disease show clinical improvement during the second and third trimester as evidenced by a reduction in maintenence steroid requirement (9).

All of the measurements of plasma steroids and their urinary metabolites in our patient were normal or slightly elevated. Our case demonstrates that pseudotumor cerebri can occur in the last trimester of pregnancy and that there is no specific period of gestation which predisposes to its development. Our case also tends to disprove the suggestion that pseudotumor cerebri in pregnancy is due to steroid insufficiency, thus undermining attempts at finding a single hormonal condition which may predispose to pseudotumor. It is conceivable that there are other, as yet unknown factors, hormonal or otherwise, at work during pregnancy that may predispose to pseudotumor, but the suggestion that the search for such a factor be confined to the first or second trimester (5, 6) warrants reevaluation.

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UNUSUAL PROBLEMS IN SURGERY

A. ROBERT BECK, M.D., Editor

Synchronous Perforation of Jejunal Diverticulitis

Submitted by

JEFFREY S. FREED, M.D., PINKUS H. SZUCHMACHER, M.D., AND GREGORIOS CHRISTODOULIDES, M.D.

Abstract

Until recently, the impression of Sommering (1974) and Cooper (1807) that jejunal diverticula were innocuous was accepted by the medical community. The literature of the last three decades had refuted this concept (1–4). We present a case to demonstrate that these curious anatomic entities may actually be the site of major clinical complications, specifically perforation and peritonitis.

Case Report

On 1-18-76, J. O. (B. H. #482709) a severely dehydrated acutely ill 76-year-old female was admitted to the Medical Service of Brookdale Hospital with a two-day history of abdominal pain, vomiting and constipation, associated with increasing lethargy. Her history included an appendectomy 15 years prior to admission. Physical examination revealed a pulse rate of 110 beats per minute, blood pressure of 100/60 mm/Hg, and temperature of 100.6°F. Her lungs were clear and her heart sounds were distant. The abdomen was markedly distended and tender, with rebound and absent bowel sounds. The patient was confused. The hemoglobin was 10 gms %, and blood urea nitrogen 88 mg %. Abdominal x-rays showed an ileus pattern with no free air. In spite of rehydration and intravenous antibiotics, the patient's condition worsened and exploratory laparotomy was performed.

At surgery, adhesions in the right lower quadrant were lysed. Multiple diffuse diverticula were noted on the mesenteric border of the small bowel. There was proximal distention and thickening of the bowel wall. Diverticulosis coli was presented. In the mid-jejunum, two discrete perforated diverticula with marked edema and thickening of the mesentery were noted (Fig. 1 and 2).

One diverticulum was locally resected and the bowel was imbricated. The second perforation was relatively larger and a segment of jejunum was resected.

The postoperative course was unremarkable except for a superficial wound infection. The pathology confirmed the diagnosis of perforated jejunal pseudodiverticula.

Comment

Diverticula of the small bowel are estimated to exist in about 0.3 to 1 percent of the population. Colonic diverticula (4). These lesions are also present in 50% of the patients though generally considered inconsequential, may give rise to

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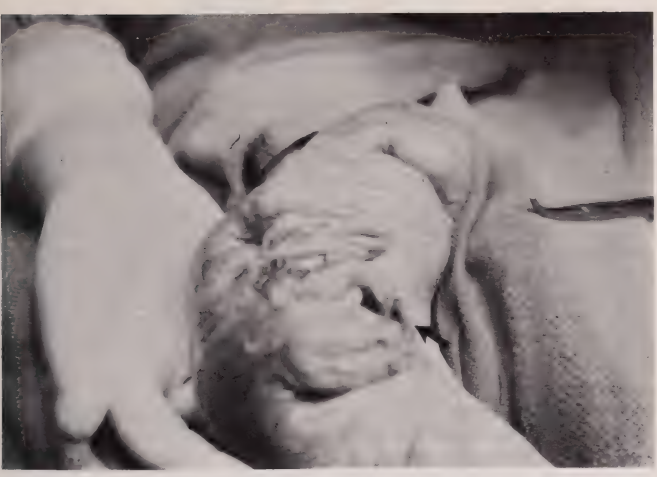

FIG. 1. Free perforation of jejunal diverticulum.

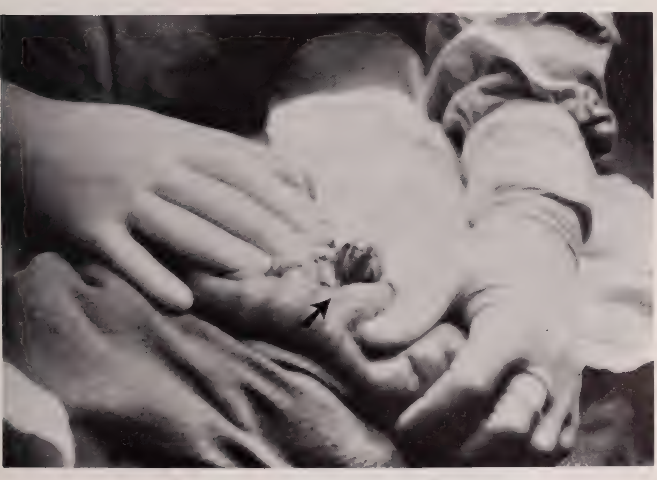

FIG. 2. Intramesenteric perforation of jejunal diverticulum.

complications of an emergent or chronic nature, including generalized peritonitis, localized abscess, adhesions, obstruction, concretion formation, hemorrhage, traumatic rupture, volvulus and macrocytic anemia (5).

Although the most common subjective complaint associated with the lesion is dyspepsia, intestinal obstruction remains the most common surgical emergency.

Our case demonstrates one of the extremely rare complications of this condition: Concomitant perforation of two separate diverticula. Despite the thin walled nature of these pseudodiverticulum (lacking a muscle coat), there have been less than 50 reported cases of perforated jejunal diverticulitis (4).

There is no single etiologic factor to explain the pathogenesis of these supposed pulsion diverticula. However, several concurrent features exist in these patients including a significant incidence of pseudodiverticula in other locations and gastrointestinal conditions associated with hyperperistalsis. In our patient, there were adhesions distal to the diverticula with proximal small bowel distention and thickening of the bowel wall compatible with chronic partial small bowel obstruction.

An almost unique feature of our case is the simultaneous perforation of two diverticula. In Herrington's (6) series a contributing factor to the mortality rate of 21% was the failure to recognize a second discrete diverticular perforation at laparotomy. Even if a definite perforation is identified, a thorough search of the entire small bowel should be performed to identify a second lesion. Multiple areas of the mesentery may be inflamed and edematous secondary to the peritonitis. However, sequential examination with dissection of the mesenteric border of the bowel must be accomplished if the slightest suspicion of an occult perforation exists.

Summary

There is a significant incidence of jejunal diverticulosis with a minimal incidence of diverticulitis and perforation. When this surgical complication is encountered, a thorough search of the bowel is necessary to avoid overlooking a second perforation. A case of synchronous perforation of two jejunal diverticula is presented, and the condition is briefly reviewed.

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Transient Diabetes Insipidus following Penetrating Thoracic Trauma

Submitted by

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Abstract

A case of transient diabetes insipidus without head injury following penetrating thoracic trauma is presented. The normal physiology and pathophysiology of the posterior pituitary gland is discussed. A possible etiology for this syndrome is a low flow state involving the blood vessels of the neurohypophysis. The diagnosis of diabetes insipidus is relatively simple with the aid of specific laboratory tests. The clinical course is rarely fatal, but severe derangements in electrolyte balance can result in increased morbidity. The treatment includes intramuscular Pitressin and intranasal application of neurohypophyseal extract.

A recent report of diabetes insipidus following penetrating thoracic trauma by Machiedo et al (1), has stimulated the report of a case recently encountered at Elmhurst General Hospital. All the cases reported by Machiedo proved fatal, and the pathological findings of the pituitary at post mortem examination demonstrated coagulation necrosis of the anterior pituitary and thrombosis of the venous plexus surrounding the pituitary capsule. The common factor in each case was a shock state. A similar case recently presented to our institution, developed transient diabetes insipidus and the patient survived. Sudden marked polyuria and polydipsia should alert the clinical surgeon to the possible diagnosis of diabetes insipidus. A careful review of the patient's intake plus a few simple laboratory examinations will allow for early diagnosis and proper treatment.

Case Report

S. P., a 34-year-old Puerto Rican male was admitted to The Elmhurst General Hospital emergency room on September 4, 1975, with a gunshot wound to the left second intercostal space in the mid-clavicular line. Vital signs revealed an unobtainable B.P., pulse of 140 beats/min, and temperature of 37°C. The patient was extremely agitated, but responded to verbal commands. On physical examination, there were decreased breath sounds in the left chest, complete paralysis of the lower extremities, with a sensory level at T10, and no exit wound. Chest and flat abdominal radiographs showed a left hemothorax, bullet fragments on the left side at the 10th thoracic spine level, and the first lumbar spine on the right side. Intravenous volume replacement, 2000cc of Ringer's lactate and 500cc albumisol, was started, and the blood pressure returned to 120/80. A chest tube was inserted in the sixth intercostal space along the posterior axillary line with an immediate return of 1500cc of blood. The patient was transferred to the surgical intensive care unit. During the next hour, the patient drained 300cc of blood through the chest tube and was taken to the operating room where a left thoracotomy revealed the bullet had entered the apex of the left lung and exited from the posterio-medial aspect of the left lower lobe. A mediastinal hematoma was found which was secondary to bleeding from the paravertebral vessels. In the immediate postoperative period, the vital signs were stable with a urine output averaging 80cc/hour and a sp. gr. averaging 1.019. Twenty-seven hours after the surgery, the urine output increased to 600cc/hour with a sp. gr. of 1.002. The patient complained of extreme thirst. Careful survey of the patient's fluid balance from admission to development of the polyuric state revealed a total intravenous intake of 8,405cc with an output of 7,610cc. The urinalysis was negative for glucose and albumin. Serum sodium, potassium, chloride, calcium, glucose, BUN and creatinine were normal. Serum osmolality was 286, and the urine osmolality was 150. The CVP varied between 0 and 3cm H_2O. Ten units of Pitressin injected intramuscularly markedly decreased the urinary output to 50cc/hour with an increase in urine osmolality to 785. After four hours, the urinary output again increased to 600cc/hour. Another dose of ten units of Pitressin IM decreased the urine output to 90cc/hour with an osmolality of 630. Over the next 12 hours, the patient's urine output stabilized around 100cc/hour (Fig. 1). The patient has needed continued hospitalization for respiratory and neurological complications.

Discussion

"Diabetes insipidus is a rare disease, characterized by polyuria and polydipsia, which results from lack of the antidiuretic hormone, arginine vasopressin" (2). This definition excludes not only renal defects such as high output renal failure and "nephrogenic" diabetes insipidus, but also compulsive habitual water drinking which is frequently difficult to differentiate from true diabetes insipidus.

Neuropharmacological advances have allowed the medical practitioner added insight into the basis of diabetes insipidus. In 1913, two independent

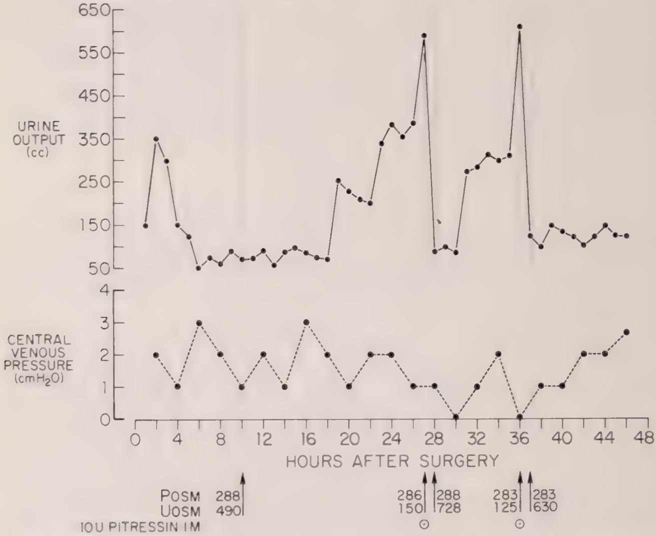

FIG. 1. Time relationship of urine output, central venous pressure, plasma and urine osmolalities before onset of diabetes insipidus and following intramuscular Pitressin.

researchers, Farini and R. von den Velden, related the antidiuretic effect of posterior pituitary extract to the physiological aspects of water metabolism. Further research delineated two active vasopressins (3), both of which are cyclic polypeptide amides- arginine-vasopressin(II) and lysine-vasopressin(III) (Fig. 2).

Although some controversy still exists, the neurohypophysis is generally considered to be the storage depot for the neurosecretory cells of the anterior hypothalmus. Cell bodies originating in the supraoptic and paraventricular nuclei of the anterior hypothalamus pass into and through the pituitary stalk to terminate in the neurohypophysis. If chemical assay of the amount of neurosecretory hormone in the anterior hypothalmus and the neurohypophysis is performed, the quantity of neurohormone in the latter is several times greater (3). This evidence confirms the depot function of the neurohypophysis.

The releasing mechanism of arginine vasopressin was first defined by the research of Verney in 1947 (4). His meticulous study delineated cells in the anterior hypothalamus which are exquisitely sensitive to changes in osmolality. He was able to show a direct relationship between ADH release and changes in plasma osmolality. A variation in osmolality of only 2% has been shown to be an effective stimulus for release of ADH (5). Volume receptors located in the right atrium, aortic arch, and carotid arteries, which are sensitive to changes in the extracellular fluid volume, are also intricately involved with the release of ADH. A fall in the extracellular fluid volume results in an immediate rise in circulating ADH.

The renal organ is divided into the cortex and the medulla. The medullary portion is more hypertonic than the cortex, secondary to an active "sodium pump" mechanism in the distal loop of Henle. Vasopressin acts in the distal tubule and the collecting duct in the medullary portion to increase its permeability to water (6), thus allowing the osmotic gradient to passively pull water from the tubules. The exact mechanism for the change in permeability is not known, but cyclic AMP has been suggested to be essential for this action.

The clinical classification of diabetes insipidus as set forth by Randall et al. in 1959 (7) has proved to be a valuable clinical guide (Fig. 3). Regarding primary diabetes insipidus, the idiopathic type makes up the majority of the cases. It may begin at any age and is equally distributed between the sexes. By contrast, the familial type is rare and usually begins in infancy. Both types show a marked decrease in the quantity of neurons in the supraoptic and paraventricular nuclei (2, 7, 8). The most common etiology of secondary diabetes insipidus has changed in recent years. With the advent of sophisticated neurosurgical techniques and high speed travel, postoperative and traumatic causes are far more common etiologies of diabetes insipidus than tumors (2). The widespread use of potent antibiotics has made an infectious etiology relatively rare.

CYS—TYR—Phe—Glu (NH2) —CYS—PRO—ANG—Gly (NH2)

FIG. 2. Structure of arginine vasopressin.

- I. Primary Diabetes Insipidus
  - A. Familial
  - B. Idiopathic
- II. Secondary Diabetes Insipidus
  - A. Trauma
    - 1. Accidental
    - 2. Surgical
  - B. Neoplasm
    - 1. Primary
      - a. Pituitary
      - b. Craniopharyngioma
      - c. Meningioma
      - d. Epidermoid
      - e. Dermoid
      - f. Teratoma
      - g. Chordoma
      - h. Pinealoma
      - i. Optic Glioma
      - j. Giant Cell Tumor of Bone
    - 2. Metastatic
  - C. Vascular Disease
  - D. Infectious Disease
    - 1. Abscess
    - 2. Granulomatous Infections
    - 3. Encephalitis
    - 4. Meningitis
  - E. Systemic Disease
    - 1. Sarcoidosis
    - 2. Xanthmatosis
    - 3. Leukemias, Lymphomas & Related Diseases

FIG. 3. Differentiation of diabetes insipidus.

Although the clinical course of diabetes insipidus is rarely fatal, severe derangements in serum electrolytes and water physiology may develop. The normal plasma osmolality averages 280 ± 6 mOsm per Kg., whereas the plasma osmolality in patients with diabetes insipidus averages 295 ± 15 mOsm per Kg (2). Although this difference is statistically significant, a fair amount of overlap makes the diagnosis difficult from this aspect alone. The urine specific gravity in diabetes insipidus fluctuates between 1.001 to 1.005 corresponding to an osmolality of 50 to 200 mOsm per Kg of water (2) with typical urine volumes of four to eleven liters/day. As long as the thirst drive remains intact, changes in the serum electrolytes will remain near normal. However, in cases of severe head trauma resulting in coma with an associated diabetes insipidus syndrome, the thirst drive may be compromised. The resultant dehydration may then lead to high fevers, mental disturbances, and death if not diagnosed and corrected.

The differentiation of diabetes insipidus from other polyurias can be accomplished in virtually 100% of all cases (Fig. 4). Any process which affects the concentrating ability of the renal unit will lead to a polyuric state. The high output form of renal failure typically produces polyuria, but the sp. gr. of the urine is usually fixed at 1.010 with the BUN and serum creatinine being

BLOOD:
Urea, Glucose, K+, Ca+, Osmolality, Creatinine
URINE:
Albumin, Glucose, Sp. Gr., Osmolality, Microscopy
X-RAY:
Skull (Sella-Tursica)

FIG. 4. Laboratory tests helpful in the diagnosis of diabetes insipidus.

evaluated. Hypokalemia and hypercalcemia produce polyuria, but the urine is not persistently dilute, and blood determinations will readily make the diagnosis. Nephrogenic diabetes insipidus is an inherited disease of infancy which is secondary to a defect in the tubules' response to ADH. Atrial tachyarrythmias can cause a decrease in renal sodium and water reabsorption with resultant polyuria, but simple electrocardiogram can be diagnostic (9). Diabetes mellitus can manifest a polyuric state by producing an osmotic diuresis. The urine osmolality is low, but the urine sp. gr. is high secondary to glucosuria. Blood and urine sugar sampling is diagnostic. Primary polydipsia or excessive habitual water drinking can be difficult to differentiate from diabetes insipidus. However, a prolonged water deprivation test will usually differentiate between the two disease states.

The investigation of renal and neurohypophyseal physiology has led to the development of several special procedures which test the body's ability to respond to osmotic stimuli. The simplest is the water deprivation test. If the condition of the patient permits, water intake is restricted. The test is terminated if 3% of the body weight is lost. The normal response to water deprivation is a urine output of less than 30cc/hour with a sp. gr. of 1.020 or greater (osmolality greater than 800 mOsm Kg.), whereas a patient with diabetes insipidus will continue to excrete large volumes of isotonic urine. Another effective test has been described by Moses and Miller, which uses the combination of dehydration and vasopressin (10). They report that every patient will reach a "plateau" when measuring urine osmolality. Patients with normal neurohypophyseal function will not increase the plateau urine osmolality after the injection of five units of vasopressin. By contrast, a patient with ADH insufficiency will increase the urine osmolality. An increase over 9% of the plateau value is diagnostic of diabetes insipidus. The intravenous infusion test, as described by Hickey and Hare in 1944 (11) is no longer used because of the danger of precipitating congestive heart failure secondary to the large volume load. The osmotic diuresis, which is inherent in the test, may also obscure the diagnosis. Intravenous nicotine has also been used, but unpleasant side effects have caused clinicians to rely primarily on the water deprivation test and its variants.

The treatment of diabetes insipidus has generally been Pitressin tannate in oil. Unfortunately, it is an impure preparation containing other polypeptide amides besides vasopressin, such as oxytocin, neurophysin, prolactin, and a corticotrophin-like peptide (12). The problems associated with long-term intramuscular injections is an obvious shortcoming of this form of therapy. The development of a nasal spray containing vasopressin has been useful for mild cases of diabetes insipidus, but the short lasting effects have negated its usage in severe cases. The recent development of 1-disamino-8D-arginine vasopressin(DDAVP), a vasopressin analogue which can be used intranasally, has dramatically improved the treatment of diabetes insipidus. This preparation is long acting, has less pressor activity than Pitressin, and is well tolerated by the patient.

The diagnosis of diabetes insipidus in this patient was based on the patient's laboratory data, and, more importantly, the elimination of other causes of polyuria. Intravenous fluid overload was ruled out because of a total overload of only 800cc. A normal BUN and serum creatinine plus a urine negative for tubular cells negated the possibility of high output renal failure. A urinalysis negative for glucose and albumin eliminated an osmotic drive as the cause of the polyuria, and the serum potassium and calcium were normal. The rapid response to intramuscular pitressin and the appropriate plasma and urine osmolalities before and after pitressin administration, prove the diagnosis of diabetes insipidus.

We can only speculate as to the etiology of this patient's transient diabetes insipidus. A previous autopsy report of patients with diabetes insipidus following thoracic trauma showed coagulation necrosis of the pituitary and thrombosis of the vascular plexus surrounding the pituitary (1). A prolonged shock state was the common denominator in each case. However, as the patient in this case report was hypotensive for at least one and a half hours, perhaps a low flow syndrome involving the pituitary vasculature resulted in a hypoxic insult to the pituitary gland. As a direct result of the hypoxia, the neural cells of the posterior pituitary, which are exquisitely sensitive to low oxygen tensions, may have been injured. This, in turn, could lead to a breakdown in the cellular releasing mechanism of ADH, which was followed by a transient diabetes insipidus symptom complex.

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THE STUDENT'S CORNER

JONATHAN STEINBERG, B.A., EDITOR

This column is a forum for medical students to comment on issues concerning medical school and medical education. The editor of this column is a third-year medical student and elected student representative at Mount Sinai School of Medicine of The City University of New York. Mount Sinai School of Medicine students are invited to take advantage of this opportunity to reach a wide and influential readership. Medical students from other schools are also invited to contribute.

Contact Mr. Steinberg through Mount Sinai School of Medicine, The Annenberg Building, Room 13-98A, Fifth Avenue and 100 Street, New York, N. Y. 10029. If you do not have time to write an entire column, you still can contact Mr. Steinberg and share your thoughts on a particular topic which perhaps can be incorporated into a future column.

David A. Dreiling, M.D.
Editor-in-Chief

The Preclinical Years—Search for Stability

Submitted by

MITCHELL S. RAPS, A.B.*

"Who is the truly wise physician?" a distinguished clinician asked us rhetorically. The answer is, "He who has learned his own limitations." This idea intrigued me. How does one go about learning his own limitations? Not long thereafter I sat down to write this editorial, seeking to explore the ambivalence of the medical student vacillating between feeling all powerful and all knowing and feeling inept and hopelessly inadequate. I had planned to trace the conflict back to childhood, when most of us were bombarded with parental suggestions of how bright we were and soon became dependent on external approval as a reinforcement of our own internal worth. I was going to talk about the occasionally surfacing haughtiness of the student and resident, as I have experienced the former and observed the latter, and explain this as a defense against feeling overwhelmed by massive amounts of material to be mastered, and/or against helplessness in the face of incurable disease. I even thought to offer speculations on the effects of the traumatic medical school admissions process (for many of us, our first exposure to rejection en masse) on our abilities to deal with this confusion. The moral of the editorial was to be that in addition to learning medicine, the student must reach some psychological equilibrium between lack of confidence and overconfidence in his (her) own ability, so that he (she) does not continuously experience the discomfort of bouncing between two extremes—elation when he (she) achieves good results, and depression when things turn sour.

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* The author is a third-year student at Mount Sinai School of Medicine of The City University of New York.

It took me a couple of days to come to my senses. The fact that I was going to coldly, clinically, analytically explore the psyche of the generalized medical student was, I suddenly realized, prima facie evidence that I was far from reconciled to my own limitations. Most of the time, to tell the truth, I can barely understand my own emotional responses to the demands of medical education. So I offer this instead as a personal statement.

I often have difficulty monitoring my own progress. When friends and relatives admire my achievements I may feel brilliant, only to be catapulted into dejection when I cannot begin to explain the pathogenesis or treatment of their assorted medical maladies. The problem is partly rooted in rebellion. It is hard for me to accept the passivity of being a student (and the associated shelter of "ignorance of inexperience") when the lure of the physician's insightful activity is so tantalizing and encompassing. But even within the context of student, my ego size changes frequently. I cannot neatly map its determinants. Several issues, however, come to mind immediately.

The first is that examinations provide less gratification and less stabilization (albeit less anxiety) than they did before medical school. Let me explain. I pass with a 65%. But is that a good grade on an imperfect test, covering one basic area (e.g. Hematology), immediately after the material has been presented, and without the complicating factor of the real-life patient situation? I cannot decide. How many of us have done well in a course (by examination standards) and then, when faced with a related problem in "Physical Diagnosis," acted as though we had never even had the course? Whether or not this is "to be expected," it hurts me to be confronted so dramatically with the enormous gap between exam paper and bedside. And on such occasions, I feel stupid. I may make silent vows to read *Harrison* from cover to cover. (While this might not be a bad idea, it reflects the ever-persistent fantasy that wisdom and intuition —traits that seem so distant—can be found within books). Funny thing, though, let me come up with a correct diagnosis once in a while, or by chance pick up an elder's error, and I might feel ready for the Dean's job. For the insecure, ambiguity means anxiety. Better to be at one of the extremes, either to revel in it, or acquiesce.

Another element concerns changing expectations about just how difficult medical school should be, academically speaking. Before I entered, I often heard the comment that medical school was going to be draining, but conceptually easy—"sheer memorization," my friends said. Well, some of it, so far, had been just that. But there have also been courses and examinations as demanding, if not more so, than those I had in college. If my performance on one of these was less satisfying than I might have liked, I usually reconciled feelings of inadequacy by writing off the test score as the result of "poor preparation" or "lack of interest in the material." Deep inside, however, I was invariably wounded—a delicate ego accustomed to being stroked by achievement stubbornly insisted that I should have been able to do better regardless of how prepared (within reason) or motivated I was. This is a very difficult state to admit to publicly. For me, the saving grace is that I honestly do not feel that intellectual snobbery, conceit, is the problem. Rather, I think that I have yet to fully appreciate, on a gut level, how subtle medicine can be at times. I have a feeling that this coming year (the clinical rotations) may help in that regard. But in retrospect, I never had trouble in college recognizing the inherent subtlety of say, mathematics or physics. Without question, these fields allow for creativity and elegance, which makes their study all the more enticing. Medicine, thankfully, shares in these qualities. But as for everything, a price is paid. Put simply, the ability to think as a doctor should be achieved only with very hard work.

While pondering all of this, something else occurs to me. Perhaps the internal chaos is merely good old narcissism rearing its ugly head. The truth is that in my future practice some patients (perhaps many) will get better on their own. Others will remain ill or die despite my best intentions, or despite the best care that I or anyone more qualified could provide. Our "cures" are not always personal triumphs, our "losses" not always personal failures. Maybe my brilliance or ignorance is not going to be the central issue in my being of use to my patients. I suppose that it will be easier for me to treat a patient if my own wellbeing is not a function of his. And it will probably be easier for the patient not to have me to worry about. The psychological equilibrium that I mentioned earlier seems ever more important.

Student Section

Study of an Outbreak of Acute Gastroenteritis in Infants and Young Children in Three Voluntary New York City Hospitals*

ATHANASIA APOSTOLOPOULOS, B.S.

Abstract

In November, 1976 an outbreak of acute gastroenteritis (G.E.) occurred in the pediatric population served by three New York hospitals (Mount Sinai, Beth Israel, and Columbia-Presbyterian Babies Hospital). The total number of G.E. admissions was 108, being the highest in the last quarter (October, November, December) for the past three years (1974, 1975, 1976). This high winter incidence and the absence of bacterial enteric pathogens in stool highly suggested a winter rotavirus G.E. Sixty percent of the children were in the 6 month-3 year age group, 59% males, 68% Hispanic. Presenting symptoms were: watery diarrhea (94%), vomiting (85%), fever (50%), and lethargy (24%). One hundred and six children were dehydrated on admission, 48% hyper-, 48% iso-, and 4% hypotonic. Seventy-six percent of the children that developed hypernatremia were given an oral electrolyte solution prior to admission, and the difference in rates between this group and the group that received the solution and did not develop hypernatremia was highly significant ($p < .01$). Possible causes of this high incidence of hypernatremia and preventive measures against G.E. are discussed.

Introduction

Acute gastroenteritis in infants and young children is common throughout the world; in India alone 1.4 million infants die annually from noncholera diarrheal disease (1). In the United States, diarrhea was at one time one of the leading causes of death in infancy. In New York City in 1889 31% of the 10,527 deaths were due to "cholera infantum" (2). Despite a dramatic reduction in morbidity and mortality in the U. S., several cases continue to present serious therapeutic problems. Diarrhea may be caused by bacteria (i.e., Salmonella, Shigella, pathogenic strains of E. Coli, vibrio cholerae, clostridium perfrigens, Staphylococcus aureus toxin) (3), viruses (entero- and adenoviruses), by parenteral infection or by noninfectious factors (allergy, emotional, dietary, or G.I. tract abnormalities). Lately, evidence has accumulated that viral diarrhea occurs more commonly than it was thought in the past, and bacterial pathogens cannot be isolated in stool in 75% of cases (11).

More recently, a specific virus has been identified which seems to be the most important etiological agent of acute G.E. in children throughout the world (4–7). It is thought to be a double stranded RNA virus and has been called orbivirus, reo-like virus, duovirus, rotavirus, and infantile G.E. virus (5, 7–10). Stools may contain 10^9–10^{10} particles/gm of feces (1) and are more often encountered in winter (4, 6), during which time the virus may be detected in up to 73% of patients (5). Rotavirus has been suggested as being the major pathogen associated with winter G.E. (4), affecting both sexes equally and predominantly children aged between 6 months and 3 years (6). The incubation period is 48 hours followed by vomiting, watery diarrhea, cramps, and low grade fever. The disease usually resolves within a few days, although it may progress to severe dehydration, collapse, and death (7). The virus can be detected in stool by electron microscopy (12). Naturally the ultimate goal is prevention, and a vaccine has been developed that reduces the incidence of the disease in calves (1).

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* Originally submitted as a research paper for the Community Medicine clerkship at Mount Sinai School of Medicine (CUNY), New York, N. Y. 10029.

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Diarrhea, regardless of etiology, produces fluid and electrolyte abnormalities such as dehydration, acidosis, altered K+ levels and in some cases hyperelectrolytemia. Infants frequently develop hypernatremia which may produce neurological manifestations (meningeal signs, seizures, irritability) and may cause permanent brain damage. Clear fluids and electrolyte solutions (Pedialyte or Lytren) are given orally, i.v. therapy given to severe cases only (13).

Materials and Methods

In November, 1976 an outbreak of acute gastroenteritis occurred in the pediatric population served by three New York City hospitals (Mount Sinai, Beth Israel, Columbia-Presbyterian Babies-Hospital). A total of 108 G.E. patients was admitted to the three hospitals. The inpatient and outpatient records of these children were examined for: (1) Age, sex, ethnic group, (2) Date of first visit to the acute care clinic, presenting symptoms and signs, and their duration prior to that visit, other concomitant infections, (3) High risk factors other than age (i.e., prematurity, chronic disease, post-surgical conditions), (4) Therapy at the acute care clinic, (5) Date of admission with diagnosis, type of dehydration, admission serum electrolytes ($Na+$, $K+$, Cl^-), bacterial pathogen isolation.

The admission records of the three hospitals were examined for: (1) Number of admissions in the months of October, November, December of the years 1974, 1975, 1976, (2) Number of G.E. admissions in the same months and years, (3) Number of G.E. admissions on each day of November, 1976.

Results

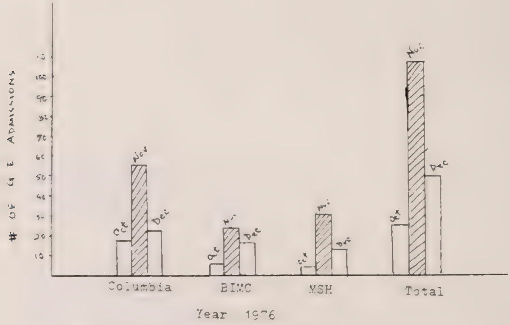
One hundred and eight children with G.E. were admitted to the three hospitals in November, 1976, 55 at Columbia-Presbyterian (9% of total admissions for that month), 23 at Beth Israel (21% of total admissions), and 30 at Mount Sinai (39% of total admissions). For all three hospitals this was the highest number of G.E. admissions over the three-year period (1974, 1975, 1976) for the three months examined (October, November, December) (Table I). Fig. 1 shows the percentage of G.E. admissions in the three months in 1976 with a peak seen in November. Sixty-eight percent of the cases were admitted in the second half of the month with a peak on November 21. Sixty-five children (60%) were in the 6 month-3 year age group, 63 males (59%), 73

TABLE I

	Columbia Presbyterian				Beth Israel Med. Center		
	Total Admiss.	G.E. Admiss.	% G.E. Admiss.		Total Admiss.	G.E. Admiss.	% G.E. Admiss.
1974				*1974*			
Oct.	306	6	2%	Oct.	98	4	4%
Nov.	442	9	2%	Nov.	94	4	4%
Dec.	489	26	5%	Dec.	114	10	9%
1975				*1975*			
Oct.	457	5	1%	Oct.	109	6	6%
Nov.	466	10	2%	Nov.	95	5	5%
Dec.	496	23	5%	Dec.	92	12	13%
1976				*1976*			
Oct.	650	18	3%	Oct.	91	5	5%
Nov.	620	55	9%*	Nov.	110	23	21%*
Dec.	619	21	3%	Dec.	92	16	17%

	Mount Sinai		
	Total Admiss.	G.E. Admiss.	% G.E. Admiss.
1974			
Oct.	55	3	5%
Nov.	47	1	2%
Dec.	54	8	15%
1975			
Oct.	69	4	6%
Nov.	46	3	7%
Dec.	70	13	19%
1976			
Oct.	64	3	5%
Nov.	76	30	39%*
Dec.	75	13	17%

(G.E. = Gastroenteritis)



BIMC = Beth Israel Medical Center

MSH= Mount Sinai Hospital

FIG. 1. Gastroenteritis admissions at the three hospitals in the last quarter of 1976

Hispanic (68%). Presenting symptoms and signs included watery diarrhea (94%), vomiting (85%), fever (50%), lethargy (24%), irritability (2%), and bloody diarrhea (0.9%). Fifty-four percent of the children had symptoms for 3 or more days before they were seen for the first time at the acute care clinics (44% at Columbia, 57% at Beth Israel, and 70% at Mount Sinai) (Fig. 2).

High risk conditions other than age included one baby with failure to thrive, one with sickle cell disease, two with asthma, one with a colostomy and HbH disease, one with an ileostomy, and one post-resection of a jejunal web. Concomitant infections included 12 cases of otitis media. No bacterial enteric pathogens were isolated. At Columbia there was a boy with previously diagnosed Salmonella G.E. and at Beth Israel another with previously diagnosed giardiasis. Thirty-eight children were admitted the first day they were seen at the clinics and were started on i.v. therapy. The difference in rates of the average time between the first clinic visit and the time of admission was significant ($p < .01$). Mount Sinai was found to have the highest delay of one or more days with three children (10%) admitted in a state of shock.

The type of dehydration on admission is shown in Table II. At Columbia and Beth Israel the majority of cases were isotonic (i.e., Na = 136–145 mEg/L), whereas at Mount Sinai 86% were hypernatremic (i.e., Na > 145 mEg/L). From a total of 106 dehydration cases 48% were hyper-, 48% were iso-, and 4% were hypotonic (Na < 136 mEg/L). Prior to admission 70 children were treated on an ambulatory basis at the clinics, 20 of which (29%) received orally glucose

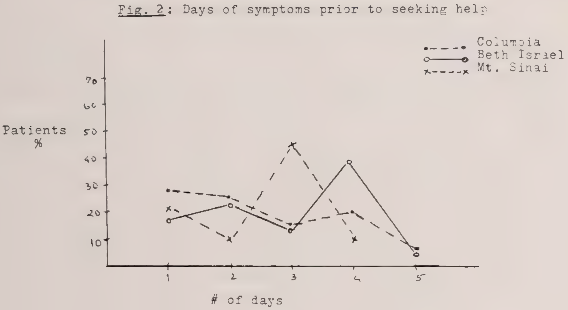


FIG. 2.

TABLE II

Type of dehydration on admission

	Columbia	BIMC	MSH	Combined (Total 106deh.)
Hypertonic (Na > 145) mEq/L	22 (41%)	4 (17%)	25 (86%)	51 (48%)*
Isotonic (Na = 136–145)	29 (54%)	18 (78%)	4 (14%)	51 (48%)
Hypotonic (Na < 136)	3 (5%)	1 (5%)		4 (4%)
No dehydration	1		1	2

in water, clear fluids, or diluted milk formula. Fifty children (71%) were given an oral electrolyte solution, Pedialyte or Lytren [22 out of 42 (52%) at Columbia, 5 out of 15 (33%) at Beth Israel, and 23 out of 25 (92%) at Mount Sinai]. Thirty-nine or 76% of the children that developed hypernatremia were given an oral electrolyte solution prior to admission. Only 11 children that received the solution did not develop hypernatremia. The difference in rates between these two groups that received an oral electrolyte solution was found to be highly significant ($p < .01$). No significance was found between age <6 months and the development of hypernatremia.

Discussion

The study shows that there was indeed a significant increase in the number of acute G.E. admissions in November, 1976 in all three New York City hospitals, being the highest in the last quarter (October, November, December) for the years 1974, 1975, 1976. In this case the definition of an epidemic can be applied as "the occurrence in a community . . . of a group of illnesses of similar nature clearly in excess of normal expectation" (16). This high incidence in November, being continued to a degree into December, along with the fact that no bacterial enteric pathogens were isolated, highly suggests a winter rotavirus G.E. (4, 6). In addition, the majority of cases were in the 6 month-3 year age group, which is the age group mostly affected by rotavirus G.E. (6). Hispanic children were predominantly affected, which, however, falls into the usual percentage of Hispanic children served at these hospitals. Watery diarrhea, vomiting, and fever were the commonest presenting symptoms which are also the major symptoms in rotavirus G.E. (7).

There was a considerable patient delay in seeking help with 24% of children being lethargic when first seen at the clinics, 2% showing irritability, and at Mount Sinai 10% being admitted in a state of shock. Thus, the question is raised about public education, prophylaxis and service availability. Also, a significant ($p < .01$) difference in the rates of the average time between the first clinic visit and the time of admission was found, which along with the severity of certain cases raises the question about prompt admission and early i.v. therapy (14).

There was an unusually high number of cases of hypernatremic dehydration. It is of interest that at Mount Sinai the majority of children (86%) were hypernatremic, and also the majority of children treated on the ambulatory basis were given Lytren. For all three hospitals combined a significant ($p < .01$) difference in rates between the children that received an oral electrolyte solution and developed hypernatremia and the children that received the solution and did not was found. "Epidemics" of hypernatremic dehydration have been seen periodically related to the feeding of improperly diluted powdered Lytren (14) or excessive feeding of properly prepared Lytren (15), which in the 1950's led to the reevaluation of the oral electrolyte solutions prescribed (14). Nowadays, the $Na+$ content of Lytren has been halved by Mead Johnson (25 mEq/L of Na), and it is no longer a powder (ready-made solution), but in the usual dilution Lytren is ⅓N tonicity of the extracellular fluid. Although Lytren by itself may not be a major contributory factor in the observed increase in hypernatremia, the following should be considered: (a) there was a considerable delay in bringing the children to the clinics, (b) sometimes there was a delay in admission, the children being treated with oral solutions only, (c) other concentrated solutions or milk may have been offered to the infants at home, and (d) inadequate instructions about feeding may have been given to mothers.

From the above it can be seen that prevention should be the ultimate goal. A useful experience comes from a report from the Indian Health Service in Arizona, where G.E. morbidity was decreased by the early identification of infants in high risk and by a 30-minute educational session between the parent and a paramedic (17). Perhaps a similar educational task could be used in informing parents about diarrhea and its dangers during the first well-baby clinic visit, and the potential prevention provided by breast feeding should be emphasized (7). The public should also be educated about contagiousness and prophylaxis. Only through adequate preventive measures will the morbidity and mortality from infantile gastroenteritis be reduced to a higher degree.

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Student Section

The Knowledge, Attitudes, and Experience of Medical Personnel Treating Pain in the Terminally Ill*

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Abstract

A multiple choice, true/false survey was conducted to assess the knowledge, attitudes, and experience of medical personnel engaged in the care of the terminally ill. The questionnaire focused on the management of pain by narcotic analgesics, especially the use of newer modalities of pharmacotherapy. Surgical residents, Fellows in Neoplastic Disease and Senior Clinical Nurses made up the sample population. The results indicated a lack of knowledge of not only the newer methods of pain management, but also of the fundamental principles governing analgesic therapy. Physicians and nurses overestimated the risks and dangers of physical dependence and addiction. They, however, assessed themselves as having sufficient knowledge, with the assistance of senior staff, to deal with most problems of terminal care. Surgical residents and nurses, in response to "attitude" questions, indicated that they believed that most patients are over- rather than under-medicated. Although their aim in pain management was to provide complete or near complete analgesia and they recognized the role of anxiety in pain, their approach to analgesic therapy indicated a lack of knowledge of strategies to minimize anxiety, thus preventing them from providing optimal pain relief.

Introduction

Symptoms:	Chronic pain
Diagnosis:	Cancer, metastatic
Prognosis:	Terminal
Therapy:	Demerol 75 mg. I.M. q4h prn

For the above patient, the diagnosis and prognosis cannot be altered by medical intervention. But what about his medication? Is this the best therapy, palliative as it may be, that can or should be provided? As a medical student on the wards of a major teaching hospital, I was struck by what I considered the haphazard manner in which terminally ill patients were cared for. In my experience, many patients seemed to be continually complaining of varying degrees of pain. As a pharmacologist, with a specific interest in narcotic analgesics, I became curious as to the rationale behind the apparent reluctance of housestaff to treat these patients with opiates. It seemed to me that symptomatic relief could have been provided these patients by initiating treatment with narcotic analgesics. Those patients requiring analgesics almost invariably were given demerol and only when their demands became intolerable were they placed on more potent analgesics.

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* This paper was originally submitted in partial fulfillment of the Third-Year Clerkship requirement in the Department of Surgery, Mount Sinai School of Medicine of The City University of New York.

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After discussions with a number of house officers, I began to suspect that the type of medical management afforded the terminal patient in a teaching hospital was a consequence of the interplay of several factors. On most medical/surgical teaching services, all medication orders are written by the junior housestaff. Dialogues concerning the rationale behind different modes of pharmacotherapy often continue at great length. Yet despite the prevalence of "pain" as a chief complaint among ward patients, relatively little if any time was spent discussing the management of chronic pain, especially in the terminally ill. As a consequence, decisions concerning the care of the terminal patient were made on an ad hoc basis, the only apparent goal being to keep the patients from becoming nuisances. Yet the housestaff I encountered appeared to lack the basic knowledge of analgesic drugs and their actions necessary to accomplish even this limited goal.

Other authors have sought to document that patients in pain receive inadequate treatment. In a now classic investigation, Marks and Sachar (1) studied the treatment of medical patients with narcotic analgesics. The authors, psychiatrists in a large teaching hospital, became interested in the subject following numerous instances in which consulting psychiatrists were called to see medical patients because of "marked emotional responses to pain, despite treatment with narcotics." To their surprise, they found in "virtually every case" that the patient was not being adequately treated with analgesics. On questioning, the housestaff were reluctant to increase or change pain medication, yet when such changes were eventually instituted, invariably the symptoms were relieved.

Marks and Sachar (1) subsequently designed a two part study consisting of 1) interviews and chart reviews of medical patients in pain and 2) a questionnaire for physicians designed to elicit attitudes and information regarding the use of narcotic analgesics. The patients interviewed were suffering from a wide variety of diseases. They found that most of these patients were experiencing serious discomfort, sufficient to produce sleeplessness, crying and persistent anxiety. In the majority of those patients receiving medication for the chronic pain of terminal malignancy, minimal doses were prescribed.

In replying to the housestaff questionnaire, most residents and interns agreed that their goal in treating patients in pain was to alleviate the pain sufficiently so that the patient experienced "no distress." Why, then, were they (medical housestaff) not successful in achieving their stated goals when it was clear that by increasing the dosage and/or frequency of pain medication they could alleviate a large measure of patient suffering?

Marks and Sachar (1) attributed the failure of physicians to provide adequate pain relief to several factors, related to pharmacologic knowledge and misconceptions regarding addiction liability. When questioned on the use of narcotics for a variety of conditions, e.g., acute myocardial infarction, the physicians stated they would employ higher doses than were actually prescribed for the patients studied in the chart review. Even so, the doses of narcotics selected by the housestaff in the questionnaire were often well below the recommended therapeutic range. In addition, doctors overestimated the duration of action of the most commonly prescribed drug, demerol (meperedine).

The housestaff questioned also entertained several misconceptions about the nature of drug addiction and of the addiction liability of narcotics in medical patients. They confused physical dependence with addiction in in-hospital narcotic use while underestimating the incidence of minor withdrawal symptoms following short term opiate administration.

With respect to terminal patients, more than a fifth of the doctors would not increase pain medication following increased demands by patients that they were not getting relief. This correlated with their interview findings that 4 of 7 patients with terminal malignancy were experiencing moderate to severe pain.

In further analyzing their results, Marks and Sachar (1) found a strong correlation between a physician's estimation of addiction liability and his reluctance to prescribe high doses of analgesics. Marks and Sachar concluded on the basis of their survey results that physicians tend to undermedicate patients in pain, partly due to lack of pharmacologic knowledge and partly due to fear of producing addiction. The authors, however, were quick to mention that their investigation left many questions unanswered regarding physicians attitudes towards the patient in pain.

The Marks and Sachar (1) study was directed toward the management of pain in a wide spectrum of disease states, for example, postoperative pain, acute myocardial infarction, as well as terminal malignancy. Clearly, the possibility of addiction in the terminal patient should evoke less concern than in a nonterminal or acute illness.

The eradication of many childhood diseases and numerous other medical advances have made it possible for seriously ill patients to survive for long periods and have provided the health care system with a rapidly expanding population of older patients, especially patients with terminal illness. As a consequence, until recently most medical personnel have had little experience in the care of the specific needs of the chronically ill. In addition, because life expectancies have been increasing, most physicians as well as lay people have had little first hand exposure to the problems of death and dying.

According to E. Kubler-Ross (2), a noted author on the subject of death and dying, this lack of exposure to death, coupled with the fear of dying, has led society to adopt a philosophy denying the existence of death. In this context the dying patient is an unpleasant reminder of that which is essentially taboo. As a consequence the dying patient is shunned and isolated.

In many ways the physicians in his dealings with the terminal patient and his family reflects societies fears and its denial of death. In many instances, patients are not told of their condition either by request of the family or by unilateral decision of the treating physician. The issue of a patient's rights and/or need to know information regarding his illness and prognosis are extremely complex. Those in favor of informing the patient of the terminal nature of his condition argue that the patient has the right to know "everything" since it is his body and his life and he should be in a position to make decisions regarding his future. Those against informing the patient generally argue that some patients are emotionally incapable of dealing with the knowledge of their condition and are being done a disservice when they are told. The arguments are of course more complicated. Regardless of whether he is informed of his condition or not, the care of the terminal patient in most teaching hospitals tends to be the same (3, 4, 5). The dying patient who, above all, needs concerned supportive care is for the most part avoided, ignored and abandoned. Why is this? There are a number of probable explanations for the less than optimal care delivered to terminal patients in teaching hospitals. As mentioned before, society is geared towards the denial of death and the search for perpetual health. Also, the training of the physician is oriented to the so called "interesting cases" which present diagnostic and therapeutic challenges. The terminal patient, in addition to being a "pariah," poses no intellectual challenge to the doctor. No sophisticated medical or surgical intervention will significantly alter the course of the disease, and the patient serves as a constant reminder of human frailty and the impotence of modern medicine (6). It is not surprising, therefore, that physicians are uneasy in their dealings with terminally ill patients. Unfortunately, possibly as a defense mechanism, this uneasiness can grow into anger. Thus, demands for pain tend to be viewed as some sort of manipulative gesture rather than a simple plea for relief from an agonizing situation (6). To justify this ostensibly punitive approach, physicians tend to minimize patients complaints, asserting that they do not wish to "snow" the patient or cause hazardous respiratory depression. Occasionally the spector of analgesic tolerance and addiction is raised and employed as a rationalization for providing suboptimal pain relief (1).

The physician's orientation to "pain" as a symptom rather than a disease entity also adds to the problem of providing therapy. Most patients present to a physician with a complaint related to some pain or discomfort. The doctor employs these symptoms in order to determine the source of the underlying problem, leading eventually to some form of therapy. Pain therefore serves as a prime clue in the search for the nature of the disease process and further provides a parameter for measuring the success of treatment.

In the terminal patient, pain has lost its value as a symptom and in fact has become a disease. Chronic or intractable pain, as distinguished from the acute pain of trauma or of myocardial infarction, is not only total and all encompassing, but is physiologically detrimental. Studies (7) have shown that chronic pain (as well as other forms of chronic stress) unlike acute or self-limited pain states, can slow the heart rate even to the point of cardiac arrest. Respiration may be affected if there is irritation or mechanical obstruction of the chest wall or diaphragm. Breathing may become shallow and rapid if pain is concentrated in the abdomen. Pain is frequently accompanied by increased metabolic rate and a rise in body temperature. Increased oxygen requirements further compound the problems.

Cancer produces pain through a variety of mechanisms. Unlike acute pain which tends to be well localized, pain in the cancer patient tends to be poorly localized and visceral in nature. Invading tumor can produce pain by impinging on pain fibers, by obstruction of a viscus, by occlusion of a vessel, or by destruction of bone and supportive tissue. Hypercalemia, often encountered in metastatic disease is also believed to produce reflex irritability and diminished pain thresholds (8). Similarly, infection, inflammation, and necrosis may produce pain directly or through the release of endogenous substances which lowered pain thresholds.

Although many sources of pain can be identified, the nature of the physiological processes underlying pain, especially those involved in deep pain have remained obscure. In classic theories, pain pathways are analogized to a "burglar alarm" system in which sensations are transmitted in a straight-line fashion from free nerve endings in the periphery through fibers whose nuclei are located in the dorsal roots. After synapsing in the cord pain information is then transmitted via the lateral spino-thalamic tracts to the thalamus and cortex (9).

Unfortunately, traditional pain theories fail to account for a variety of pain phenomena including causalgias and "phantom limb" pain. According to classic theory destruction of any part of the pain pathway should eliminate the possibility of pain perception from the affected area. Stimulation of pain-specific fibers should invariably produce pain and conversely the absence of stimulation should preclude the possibility of pain experience. Yet it has been documented many times, patients suffering from causalgias report pain from areas where no stimulus can be identified (9). Similarly amputees often experience pain in the absent or "phantom" limb. Also, there are many reports in the literature of soldiers wounded in battle reporting little or no pain from badly damaged tissues (10). Further, many neurosurgical procedures such as rhizotomy and cordotomy, and neurolytic procedures in which pain pathways are "blocked" pharmacologically, often produce only transient and partial relief from pain (11).

It was through postmortem examination of patients with neurosurgical procedures for pain relief that modern concepts of pain emerged. Patients with cordotomies were found to have destruction in fiber tracts not only directed to the thalamus but to other structures particularly in the reticular system (11). Subsequently, a number of descending as well as ascending fiber tracts were identified, connecting nerve cells in the cord to cortical and subcortical nuclei (12). Thus it became anatomically feasible that descending cortical influences could directly effect the perception of information transmitted from the periphery.

The modern theories of pain such as the controversial "Gate-Theory" of Melzack and Wall (13) stress the importance of the motivational or affective components of pain, which are believed to be mediated through descending or cortical mechanisms.

Since potent analgesics have not been found to effect the function of peripheral or ascending pain pathways, alterations in the motivation aspects of pain have been proposed as the mechanism by which narcotics produce analgesia (9). Such techniques as electric dorsal column stimulation of the cord have been employed recently on the premise that electrical stimulation can selectively disrupt or "jam" pain transmission (14).

Because it provides a convenient framework for correlating neuroanatomy and physiology, classic pain theory is usually taught as dogma in most medical schools. This simplistic view of pain physiology unfortunately can lead to serious misconceptions regarding the nature of pain and its treatment. By failing to appreciate or by discounting the importance of the motivational aspects of pain one consequently approaches pain as a purely physical process to be evaluated on an objective basis. In this context, the physician feels justified in prescribing analgesics on the basis of objective clinical findings, rather than in accordance with the subjective interpretation of the severity of the pain by the patient. In summary, then, although it is necessary for the physician to attempt to identify and eliminate the physical source of pain, it is imperative that he acknowledge that pain should be treated on the basis of a subjective report by the patient.

To distinguish between physical and psychogenic pain only creates a false dichotomy since neither the patient nor the physician can isolate the relative contribution of the factors which manifest themselves as pain.

Clearly, one of the goals in the care of the terminally ill should be to create an environment in which the patient is not exposed to conditions which tend to enhance the experience of pain. The teaching hospital environment is a milieu which provides no such conditions. As previously described, the terminal patient in a large hospital is isolated, misunderstood, and, for the most part, totally dehumanized. Very often the only contact between staff and the patient involves the request and administration of pain medication. Consequently, the experience of pain is reinforced because the patient is rewarded by the appearance of a nurse or physician. Eventually the patient assumes the "sick" role to a greater degree, becoming more and more dependent on the staff to provide his psychological as well as physical needs. As dependency increases so does anxiety. The patient becomes preoccupied with fears of dying, with fears of abandonment, and with the fear that pain will become unbearable (1, 11, 15). These fears and anxieties cannot be expressed verbally and are frequently translated into pain. A vicious circle is created in which the patient becomes more and more demanding and the staff withdraws from the patient, making him even more anxious—all of which contribute to and amplify the patient's experience of pain.

In the last few years, facilities have been established in England, then in Canada and the United States, designed specifically for the care of the terminally ill (4). The staff of these facilities were aware of the problems encountered in managing the terminally ill and sought to develop strategies which would provide the optimal quality of life for the dying patient. The techniques developed in these facilities proved to be highly successful in that terminal patients could be maintained relatively free of pain in a supportive environment. Many of these strategies, especially those involving the use of analgesics, could be applied easily in the ward setting. Yet, as discussed, newer approaches to the care of the terminally ill have for the most part not been put to use in majority of teaching hospitals.

The purpose of this study is to inquire into the knowledge, attitudes, and experience of physicians and nurses with regard to the care of the terminally ill patient, specifically the patient in pain. The goal of the study was to identify aspects of physicians/nurses training and experience which directly influence the care provided the terminally ill in their charge. Along with the presentation of the experimental results, a discussion of some of the recent advances in terminal care is presented.

Methods

A multiple choice—true/false questionnaire was prepared containing 31 questions. Respondees were asked to choose the best answer for each question; a space for comments on individual questions was provided. The questionnaire was delivered with a covering letter and instructions to medical and surgical housestaff, neoplastic fellows, and senior clinical nurses*. The mode of distribution was different for each group. Anonymity was insured and the answer sheets were coded only for specialty and year of training. The proposed study was discussed with and supported by the chiefs of both the surgery and medical services, however, only in the case of the Surgery Department were the chief residents instructed to set aside a specific time for completion of the questionnaire. The assistant director of Nursing directly supervised the distribution and collection of questionnaires in that department. Neoplastic fellows received the questionnaire in their mailboxes with a covering statement and a return envelope.

The compliance rates varied. Only a fraction of the medical housestaff completed the questionnaire. The low response rate may have been related to several prevailing conditions at Mount Sinai Hospital during the period in which the survey was carried out. First, the questionnaires were distributed to housestaff on the ward services, not to those on electives or on less active, e.g., private service, rotations. Second, the survey was performed in July, thus many interns and residents were just becoming acclimated to the hospital. In addition, the more senior residents as well as the interns were faced with a newly instituted reorganization of the medical wards. Finally the survey was distributed in the week following a strike by hospital employees. These factors would seem to satisfactorily explain the low compliance rates among the medical housestaff. However, the author contacted a number of nonrespondees. In many instances, they confided that they doubted the anonymity of the survey and were reluctant to complete the questionnaire because the questions were of such difficulty that they "looked worse" if they completed the survey than if they ignored it. Because of the nature of these replies, it was possible that those questionnaires actually completed by the medical residents might be a biased sample. As a consequence, data from the medical resident questionnaires are presented only in anecdotal form. $^{11}/_{16}$ surgeons, $^{13}/_{20}$ nurses and $^{5}/_{10}$ neoplastic fellows completed the survey for an overall compliance of 63%.

Results

Experience

The overall experience of the surgery housestaff with terminal patients was small, less than 50% had treated more than 20 patients, as compared to over 70% for nurses and 100% for neoplastic fellows.

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* Equivalent to a head nurse (greater than 3 years experience).

The major source of knowledge regarding pain management for surgical housestaff was considered to be fellow residents rather than medical school teaching or attending physicians. Nurses and Neoplastic fellows in contrast felt that practical bedside experience was the major source of their training in pain management. When faced with a problem involving the choice of pain medication, the majority of surgeons relied on the Physicians Desk Reference (PDR) rather than on pharmacology textbooks or advice from nursing staff.

When asked to assess their own competence in managing the dying patient, $^{3}/_{11}$ surgeons felt their knowledge was adequate to deal with most clinical problems; $^{6}/_{11}$ felt their knowledge was less than adequate but believed senior housestaff could assist them. One surgeon felt his knowledge to be grossly inadequate, and one surgeon felt his knowledge to be inadequate but did not consider the deficiency significant enough to warrant further training. $^{8}/_{13}$ nurses and $^{4}/_{5}$ neoplastic fellows were satisfied with their ability to care for the dying patient. Only $^{1}/_{13}$ nurses and none of the neoplastic fellows considered their knowledge of terminal care to be grossly inadequate.

Demerol (meperidine hydrochloride) was selected 2:1 over morphine and codeine as the narcotic drug of first choice for the treatment of pain in the terminally ill. $^{9}/_{11}$ surgeons based their choice of medication on prior experience with the drug rather than on the belief that the particular drug was safer with respect to addiction liability or toxic side-effects. Nursing staff showed a preference for morphine, $^{4}/_{13}$ selecting it as the drug of first choice. The preference of remaining nurses were equally divided between other drugs such as levorphanol, Percodan (oxycodone), and demerol. Neoplastic fellows showed no preference for a specific pharmacologic agent though they tended to select less potent analgesics over the more potent drugs. As with the surgeons, Neoplastic fellows and nurses prior experience was employed as the rationale behind their choice of drug.

In the Marks and Sachar (1) study as well as in the present investigation, demerol was the most often employed narcotic analgesic. The choice of demerol was based primarily on prior experience with the drug but no inquiry was made as to whether other drugs had been tried and found to be less effective. It is of interest that demerol remains the most popular analgesic even though a number of recent articles have indicated it to be one of the least efficacious drugs for the management of chronic pain (3, 6). Responses to subsequent questions on the pharmacology of narcotic analgesic provided some insight into reasons why medical personnel prefer demerol to other more effective analgesics.

Knowledge of Clinical Pharmacology of Narcotic Analgesics

Ideally a thorough knowledge of clinical pharmacology should be the basis of pharmacotherapy. The responses to the pharmacology questions in the present survey indicated a surprising ignorance of the pharmacologic principles underlying analgesic therapy.

With respect to basic pharmacology, a majority of the survey population ($^{20}/_{28}$) believed that morphine was ineffective as an analgesic when administered orally, based on its "poor absorption from the gastrointestinal tract." This response indicates a basic and significant misconception concerning the clinical pharmacology of narcotics. It is true that opiates act more rapidly and at lower doses when administered parenterally, but as Goodman and Gillman (17) clearly state "opioids are readily absorbed from the gastrointestinal tract." Furthermore many recent studies have shown that oral administration of narcotics may have distinct advantages in providing optimal pain relief for patients in chronic pain (18, 19). Why then do medical personnel have the impression that narcotics are ineffective analgesics when given by mouth? First, it is obvious that parenteral medication offers greater and more rapid relief from pain, which is certainly desirable in the management of pain in acute or self limiting situations such as following trauma. In this situation oral medication is minimally effective because of its slow absorption, and gradual onset, and lesser peak effect at equal doses. The above considerations are significant with regard to acute pain but have little bearing on the problems of chronic pain. The drawbacks of oral medication for acute pain are the very characteristics which make oral administration the ideal modality for managing chronic pain. Unlike the acute patient the chronic pain patient requires constant prolonged analgesia and not the "peaks and valleys" encountered due to the "bolus effect" of parenteral administration. The problem of gradual onset and relatively poor absorption are not significant as long as the patient receives the appropriate doses at regular intervals.

One question that is often raised concerning oral analgesic medication is: Can cancer patients in a debilitated state tolerate oral medication? Twycross (20) studied 500 patients treated at St. Christophers Hospice, a facility for the terminally ill. Over 80% of the patients required pain medication at some time prior to death. 85% of these patients were maintained on oral therapy until within 12–24 hours of death. Patients received heroin (Diacetylmorphine) in a form of Bromptons Mixture*. In a recent investigation Mount, et al (18) found oral morphine (in Bromptons Mixture) a "highly effective, flexible, safe, and convenient means of controlling the chronic pain of malignant disease."

Recent reviews of the analgesic literature such as by Halpern and Bonica (21) unfortunately, have been misleading on the issue of the oral effectiveness of narcotic analgesias. Those authors state that a 10 mg. intramuscular dose of morphine was effective in 70–90% of patients with post-operative pain but that 10 mg. was effective in only 40% of patients when administered orally as compared to 30% for a placebo. The authors suggest that the morphine's oral ineffectiveness is due to its slow absorption, concluding that "morphine should always be given parenterally." Clearly Halpern and Bonica were considering pain in the acute setting. No doubt, however the unsophisticated reader will assume from such conclusions that opiates are not orally effective regardless of the source and duration of the pain.

Marks and Sachar (1) found that housestaff tended to prescribe narcotics such that the interval between doses exceeded the time of action of the drugs employed. In the present investigation, 8/11 surgical housestaff believed that if an intramuscular injection of morphine had its maximum analgesic effect at 1 hour, it would still have half this effect after 3 hours. In contrast more than 90% of the nursing staff and Neoplastic Fellows felt that 2-2½ hours represented the point at which morphine still retained half of its effectiveness. Studies by Houde and Wollenstein (22) have shown that morphine at therapeutic doses (10–30 mg.) administered intramuscularly or subcutaneously has its maximum effect at 1 hour, falling off to 50% of the 1 hour level at 2-2½ hours and to less than 20% at 4 hours. From the response of the surgical housestaff it is not surprising that analgesics tend to be prescribed at intervals which cannot possibly provide adequate analgesic coverage. It is of interest that the nurses and Neoplastic fellows, with their greater experience, were more accurate in their prediction of narcotic time-action relationships.

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* A solution with an alcoholic base usually containing an opiate analgesic plus cocaine, and an antiemetic such as chlorpromazine.

Four out of 11 surgical housestaff members and 9/11 nurses surveyed believed that the site at which narcotics exert their analgesic action is outside of the central nervous system. Although the precise site at which narcotics exert their analgesic effect is not known, there is no evidence that morphine has any effect on peripheral nervous structures (9, 17). Most investigators believe that morphine analgesic action is localized to higher cortical centers (17) and does not interfere with pain transmission per se. The concept that morphine analgesia is a cortical rather than a peripheral process, as in local anesthesia, is central to a rational approach to analgesic therapy for chronic cancer pain.

Only 2/11 surgical residents, 2/5 Neoplastic fellows and 3/13 nurses were aware that monoamine oxidase inhibitors were specifically contraindicated when demerol is being administered. The toxic drug interaction encountered when these drugs are used concomitantly is cited in many standard references (23, 24). In contrast 2/11 surgeons and 2/5 Neoplastic fellows felt that the use of chlorpromazine with demerol was contraindicated. Most studies (5, 19) have shown that the combined use of analgesics with phenothiazines such as chlorpromazine not only counteracts the nausea associated with potent analgesics but also permits the use of smaller doses with no dimunition in pain relief.

When asked which narcotic analgesic at equianalgesic doses produced the least effect on respiratory function, only 2/11 surgeons believed there was no difference between codeine, demerol, and morphine. Three of eleven chose demerol, and 6/11 chose codeine as being the "safest" drug. Four of 5 Neoplastic Fellows but only 1/13 nurses answered that there was "no difference." These responses suggest another basic misconception regarding the pharmacology of narcotics. Virtually every study (review by Vandam (25)) has shown that when equated for effect (analgesia), there is no advantage as regards toxicity, addiction liability, etc. of one narcotic agonist over another. Yet housestaff in this study and in Marks and Sachar (1) investigation overwhelmingly prescribed demerol over morphine.

What is the basis of this preference for demerol? Several possibilities can be suggested. The history of the medical use of narcotics contains numerous accounts of the search for opiate derivatives, synthetic analgesics capable of producing analgesia without the risk of addiction. In each instance drugs initially touted to be safer than morphine were eventually found to offer no significant benefits over morphine (17). Similarly demerol was originally synthesized in Germany during World War II when access to the Turkish poppy was limited. Demerol became popular because its atropine-like action was believed to prevent the smooth muscle spasm encountered with opiates. Yet over the years no documentation has been produced that demerol induces less biliary or ureretal spasm than morphine. Most authors (17, 25) now contend that there is no advantage of demerol over morphine. Unfortunately the impression that synthetic narcotics are safer than opiates has persisted.

The preference for demerol over morphine (whatever the reasoning) is not only pharmacologically unsound, but likely contributes to the mismanagement of patients in pain. As previously discussed, demerol used in conjunction with monoamine oxidase inhibitors (and tricyclic antidepressants) leads to a toxic drug interaction. Tricyclic antidepressant as well as other psychotropic drugs, however, have been shown to be valuable adjuncts to terminal care and can be used safely with opiate analgesics. In addition, demerol when administered intramuscularly has a significantly shorter duration of action than morphine. Consequently when administered on a "q4H" basis as Marks and Sachar found to be the common practice, there is virtually no remaining analgesia well before another injection can be given. Thus patients are exposed to repeated cycles of pain-delay-injection-and-recurrence of pain. The significance of this "peak and valley" cycle to overall pain management will be discussed in detail.

A number of respondees believed that codeine was in fact a safer drug than morphine or demerol. It is true that on a dosage scale morphine is more potent than codeine, but as with demerol, when equated for analgesic effect there is no therapeutic advantage to codeine. Codeine is metabolized to morphine in the body and the codeine molecule probably has no analgesic effect (17).

Care of the Terminally Ill

When asked to what extent anxiety influenced pain medication requirements in terminal patients, 6/11 surgeons felt it was a major factor and 5/11 surgeons replied that it was a significant but not a major factor. None responded that anxiety was only a minor factor. A similar distribution of responses was obtained from the nursing and neoplastic disease personnel. Thus, medical personnel recognized the role of anxiety in modifying pain medication requirements, however, this concern was not reflected in their approach to pharmacotherapy. For example, 8/11 surgeons prescribed pain medication "prn" almost always. Nurses and neoplastic fellows also almost invariably wrote for pain medication on a "prn" basis.

What was the perceived advantage to "prn" ordering? When asked this question 5/11 surgeons, 2/5 Neoplastic Fellows, and 7/13 nurses replied that "prn" was best for patients since medications were only given as needed, thereby minimizing tolerance development and inadvertent overdosing. 4/11 surgeons and 2/11 nurses replied that convenience was the only advantage to "prn" ordering, whereas 2/11 surgeons, 3/5 neoplastic fellows, and 2/13 nurses saw no advantage to "prn" ordering but did so on instructions from senior nurses or housestaff.

Did the survey population actually believe that "prn" ordering minimized narcotic analgesic dose requirements? Surprisingly, and in seeming contrast to their responses to previous questions, only 3/11 surgeons, 2/13 nurses, and none of the Neoplastic fellows believed that ordering on an every 4 hour basis rather than on an every 4 hour "prn" basis would increase or escalate the dose requirements of patients receiving repeated injections of analgesics. 8/11 surgeons, 5/5 of neoplastic fellows and 11/13 nurses believed that patient receiving pain medications on a regular (non prn) basis would require the same or lower doses of medication.

The responses to the latter three questions present a curious paradox. Housestaff almost invariably wrote for pain medications "prn" presumably on the belief that this approach minimizes tolerance development, and overdose liability, yet the majority of them did not believe that this approach would in fact lead to a reduction in drug usage. Several explanations can be postulated. Housestaff, as discussed, rely to a great extent on senior staff with regard to choice and mode of administration of pain medication. It is likely that most housestaff do not, as a rule, question their seniors as to the reason for using "prn" ordering, but assumed that some rationale was involved. In the questionnaire, a seemingly logical (but fallacious) rationale, i.e., prevention of tolerance and accidental overdose, was provided. It is possible that despite this ostensibly satisfactory rationale, most housestaff, either through practical experience, or for some as yet undetermined reason, did not really believe that the "prn" system provided a better means of controlling drug dosage or preventing tolerance and addiction.

What are the effects of supplying pain medication on a "prn" basis? A number of recent investigations by authorities (15), (26), (27) in the field of terminal care have shown that not only is there no advantage to the "prn" system in managing the terminally ill, on the contrary, they determined that it is strongly contraindicated. In fact, the elimination of the "prn for pain" has been found to be one of the basic prerequisites for optimizing care for the terminally ill. Why should this be so? The theory behind "prn" medication is that by requiring the patient to ask for pain medication, the patient will only receive the drug "when he needs it." Further, housestaff are keenly aware of the ravages of drug addiction and likely feel that by giving patients medication only on demand they are preventing the patient from experiencing the euphoric properties of narcotics thereby lessening the risk of addiction.

It is both unfortunate and ironic that, in reality, the problem of tolerance and addiction are not alleviated by "prn" medication but aggravated. The housestaff surveyed believed that anxiety influences pain perception and experimental evidences supports this contention. For example, in studies where subjects were asked to quantify a painful stimulus, those subjects told in advance to expect a strong stimulus, invariably reported more pain than subjects not forewarned. Similarly, clinical studies have demonstrated that patients examined by a nurse or physician in a reassuring fashion following a report of pain, tended to require less medication to achieve satisfactory relief (9). Thus anxiety should be considered an integral part of the pain experience and every attempt be made to eliminate it.

When medications are prescribed "prn" the patient is essentially being told "you must reexperience the pain," i.e., you must first suffer then you will get relief. Consequently, patients are forced to repeatedly suffer pain plus the anxiety of its anticipated recurrence, as well as the uncertainty of effective relief. Each new encounter with pain therefore carries with it the memory and the fear of the previous painful episode.

The addiction liability of narcotics is believed to be related to their ability to produce euphoria and the development of psychological as well as physical dependence. Although it is not well appreciated, narcotic analgesics are rarely euphorigenic in the clinic setting (6). In the majority of "well" subjects, narcotics produce dysphoria often as a result of nausea. In the pain patient receiving "prn" medication however the administration of analgesics is repeatedly associated (in a classical conditioning fashion) with relief from an agonizing condition. Thus the drugs need not produce euphoria to establish a psychological dependence; each time the patient experienced pain he is reinforced by a reward (an injection) for his suffering.

Studies by Saunders (15) and Twycross (20) have demonstrated that terminal patients can be provided effective pain relief for long periods of time, and part of their approach involves regular rather than "prn" administration of medication. Saunders studied 900 patients admitted to St. Joseph's Hospice with a prognosis of 3 months or less. 70% of these patients were transferred from other institutions with pain as their primary management problem. Saunders believed that minimizing fear and anxiety was crucial to effective pain control. This meant totally eliminating not only the pain but its memory. To accomplish this, she decided to administer narcotics on a regular basis, which involved waking patients in the middle of the night for medication even in the absence of any complaints at that time. She found that by employing analgesics on a prophylactic basis, she could provide effective pain control in a majority of patients. Medications (heroin and an aniemetic if necessary) were administered orally for the reasons outlined previously.

The hospice setting provided a supportive atmosphere with a concerned staff experienced and oriented towards terminal care. Based on their responses to the questionnaire, in the experience of physicians and nurses, patients were only occasionally examined when a change of pain medication orders is contemplated. It is difficult of course to assess, on an objective basis the value of supportive care in the terminal patient. It is, however, not difficult to imagine the plight of the dying patient, with unexpressed fears and tensions, isolated from normal human interaction and often only vaguely aware of his disease and prognosis.

Although strictly controlled clinical trials were not performed by Saunders (15) and Twycross (27) which would have been both technically difficult as well as unethical, their findings are nonetheless impressive. Most patients were kept free from pain, alert, and oriented without being "snowed."

Often in the course of analgesic therapy, a given drug or drug regimen loses its effectiveness and a decision must be made regarding the choice of a new drug. A hypothetical clinic situation was presented in the questionnaire. Respondees were told that demerol 100 mg. I.M. q4H was no longer effective in controlling pain in a terminal patient, and given a choice of a variety of medications and dose regimens. 8/11 surgeons chose morphine 10 mg. I.M. q4H, 1 surgeon chose methadone 5 mg. p.o. q4H, and 2 chose dilaudid 2 mg. I.M. q4H, 2/5 Neoplastic fellows chose morphine 5 mg. and another 2/5 preferred dilaudid. 4/13 nurses preferred morphine 10 mg, 4/13 methadone and 4/13 levorphanol 2 mg. I.M. q4H.

Most authorities (6), (17) agree that 10 mg of morphine I.M. is equianalgesic to demerol 75 mg I.M. (equated for peak action), 10 mg methadone p.o., 2 mg levorphanol I.M., and 1.5 mg dilaudid. Five mg of morphine and 10 mg of methadone would be inadequate substitutes for demerol even if it (demerol) were still effective, assuming that the patient was "tolerant" to 75 mg of demerol it is unlikely that 10 mg of morphine would provide effective analgesia. Dilaudid and probably levorphanal at the doses indicated would probably afford the best transition from demerol. The choices made by the survey population probably reflect an ignorance of narcotic dose relationships as well as a fundamental lack of understanding of the pharmacology of addiction. For example, the selection of the lower of the two doses or morphine might be due to the false assumption that opiate analgesics are inherently more potent or more dangerous than synthetics. The drug and dose most often selected was morphine 10 mg. Morphine at this dose would probably provide no better relief from pain than the already ineffective demerol. Thus the patient would be forced to endure some degree of pain, initiating a cycle of pain-anxiety-ineffective analgesia, etc.

The introduction of the vicious circle of decreased analgesia leading to increased anxiety and even greater loss of analgesia, can also be generated by initiating analgesic therapy with a course of gradually increasing doses in an attempt to "titrate" the patient to a "minimal effective dose." This approach like the use of "prn" orders, appears superficially to be more advantageous than starting at a higher dose. Over 90% of the surgeons, nurses and Neoplastic fellows surveyed favored the "titrating" approach over the use of "high" doses from the outset.

Twycross (27) found that by starting with moderately high doses he could provide effective analgesia without patients encountering problems of tolerance or euphoria for as long as 3 months. Moreover, he found that once the patients pain was controlled that doses could be reduced until an optimal dose was reached.

The use of high or "loading doses" provides rapid and complete relief, allowing the patient to forget the memory of the pain and diminishing the fear of its recurrence. In contrast, with gradually increasing doses, the patient always carries with him the memory of last episode of pain as well as the fear of its return.

Marks and Sachar (1) asked housestaff in their survey: "In general, all other things being equal, when using I.M. analgesic medication, the most desirable end point is . . . A) the patient reports complete relief from pain for the full interval between doses; B) the patient reports enough pain relief so that the pain is noticed but is not distressing; C) the patient reports that the pain is relieved during the period of peak drug action, but is distressing at other times; D) the patient is midly euphoric but not disoriented or unresponsive; E) the patient reports the onset of pain at times when he may receive a prn injection. 100% indicated that their goal was either (A) complete relief or (B) enough relief so that it is not distressing. In our sample 4/5 Neoplastic fellows and 9/13 nurses selected (A) complete relief as their intended goal. Curiously, only 1/11 surgeons selected (A) whereas 7/11 selected (B), 2/11 selected (D) and 1/11 selected (E). Marks and Sachar did not indicate the relative fraction of housestaff in their survey selecting (A) or (B). It is tempting to speculate on the differences in housestaff and nurses as well as Neoplastic fellow attitudes which contributed to the choice of therapeutic aims. The response may only reflect the relative inexperience of the surgeons or it may be an expression of a more conservative or distrusting attitude towards the patient in pain.

Marks and Sachar (1) found that housestaff confused such concepts as addiction, psychological and physical dependence, withdrawal, etc. They overestimated the addiction liability involved in the therapeutic use of narcotics, which Marks and Sachar suggested might account for their reluctance to choose appropriate dose regimens in managing pain.

In the present investigation 5/11 surgical housestaff, 3/5 Neoplastic fellows, and 10/13 nurses felt that unsupervised withdrawal from morphine involved medical hazards equal to or greater than might be encountered with barbiturate withdrawal. It is surprising at the least that despite the emphasis in medical school curricula on drug abuse, medical personnel believed that barbiturate withdrawal with its many potential hazards represented less of a risk than morphine withdrawal, an unpleasant but essentially benign process.

Housestaff, nurses, and Neoplastic fellows grossly underestimated the possibility that mild physical dependence to demerol, as manifested by minor withdrawal symptoms, could be elicited after a week of demerol 100 mg. I.M. q4H. Thus housestaff overestimated the risks of physical dependence to narcotics while simultaneously underestimating the likelihood of its occurrence; suggesting a rather limited understanding of the nature and implications of chronic narcotics use.

The placebo effect and the use of placebos in pain management is often debated. It is well established that placebos are often as effective pain relievers as mild analgesics, e.g., Darvon (propoxyphene). Placebos have also been shown to be effective analgesics in even more severe types of pain (28). Should placebos then be used even on a trial basis in the management of pain in the terminally ill? 5/13 nurses, 2/11 surgeons, and none of the Neoplastic Fellows agreed with the use of placebos in terminal care.

The use of placebos in the terminally ill could be rationalized on several grounds, such as to treat the psychogenic component of chronic pain, the prevention of analgesic to tolerance, etc. With regard to the latter argument, Twycross (27) found that the relative risk of "escape from analgesia" through tolerance was negligible. However, the potential dangers of losing the trust of a patient, creating a situation of mistrust, fear and anxiety are very real. There are of course ethical questions regarding informed consent and the doctor/patient contract, etc. In any case the use of placebos in the management of pain in the terminally ill is short sighted from a moral and clinical perspective.

Requests for increased pain medication are commonplace in hospitals caring for the terminally ill. Such requests are a burden to the patient's family, fellow patients as well as nurses and physicians. It is a frequent and pathetic sight to watch a family member or friend forced to function as messenger, pleading with physicians and nurses for pain medication. How do medical personnel react to the constant entreaties of a terminal patient and how does the interpretation of the patients needs and their feelings about their role in the patients care influence the treatment provided? Such questions are of course difficult to answer. In order to get some insights into the doctor-terminal patient relationship, several questions were posed.

When asked the most likely explanation for a terminal patient requesting greatly increased doses of pain medication, 50% of surgeons and Neoplastic fellows and 8/13 of nurses believed the patient was experiencing increased pain. None believed the patient was a malingerer. A significant proportion (50%) of surgeons and Neoplastic fellows and 5/13 nurses believed patients requests were related to addiction (tolerance). In their studies, Twycross (27) and Saunders (15) found that tolerance development (if it occurred) only rarely accounted for increased analgesic requirements. In the overwhelming majority of cases studied, analgesic demands were related to increasing symptoms.

Asked how they would deal with a terminally ill patient receiving narcotics who experienced "euphoric" episodes, 50% of surgeons, 6/13 of nurses and 1/5 of Neoplastic fellows would decrease pain medication. 50% of surgeons, 4/5 of Neoplastic fellows and 6/13 of nurses indicated that they would continue the medication unchanged. 2/13 nurses felt the euphoria represented an organic mental syndrome or psychotic process.

Finding a terminal patient in a euphoric or more importantly complacent state of mind may be confusing and disconcerting to an inexperienced house officer or nurse. The survey results suggest that a significant proportion of housestaff and nurses would attribute such a condition to overmedication and would intervene by decreasing pain medication. Twycross (27) has found, that in his experience, patients need not become "snowed" from narcotics. Euphoria, however, can be confused with the state of "peace and serenity" achieved by some patients immediately prior to death. Kulber-Ross (2) refers to this phase of "acceptance" as the fifth and final phase of the psychological reaction to dying. According to Kulber-Ross dying patients tend to pass through a series of five phases of adjustment to the knowledge of their impending death: denial and isolation, anger, bargaining, depression and acceptance. The ultimate goal of analgesics and supportive care should be to promote the onset of the phase of acceptance which necessitates relieving the patient from preoccupation with the physical discomforts that accompany disease.

It is difficult to determine how physicians and nurses view their roles and responsibilities in the care of the terminally ill with regard to the use of addictive drugs. Marks and Sachar (1) commenting on their findings stated: "There is also some indication that prescribing a drug that might induce euphoria may even evoke psychological-counter reactions in some medical and nursing personnel. The apparent reluctance of staff to administer narcotic analgesics may have accounted for the fact that the patients in our study actually received less medication than was prescribed for them on a pro re nata basis." In order to gain some insights into the emotional significance of employing narcotic analgesics, the following question was posed. "In 1973, a study was conducted to determine the effectiveness of management of pain by housestaff in teaching hospitals. The study determined that:

A. Most patients received adequate treatment for pain.
B. Most patients received more pain medication than was necessary or indicated.
C. Majority of patients were undermedicated."

Obviously the study referred to in the question was that of Marks and Sachar (1) and the correct response was (C). Individual answers to these questions could have reflected direct knowledge of the results of the study or could have been a projection of the respondees view of how he and his peers regard their management of patients in pain. 100% of Neoplastic fellows chose the correct answer (C). In contrast, 8/11 surgeons and 6/13 nurses (and 8/12 of the medical residents completing the questionnaire) selected (B). Only 1 (nurse) chose (A). Thus the majority of medical personnel in the present investigation were not only unaware of Marks and Sachar's work, but assumed (or guessed) that the results of the study showed the exact opposite findings than were actually observed. Why then do physicians and nurses feel they are overmedicating patients in pain? Do they believe that patients are psychologically addicted to these drugs and don't require them for "real pain?" Do physicians and nurses believe that they are too easily manipulated by the complaints of the patient and through expediency "snow" patients with high doses of analgesics? Is it possible that they believe that dying should or must be painful and experienced as such?

Clearly, the responses to the latter question are the most perplexing in this study, and are open to speculation. Answers to previous questions indicated that housestaff did not believe pain medication requests were the result of malingering, yet their goal in treating pain was limited rather than complete relief from pain. It is possible that the responses to "attitude" questions were based on the respondees perception of the "correct" or "expected" answer, rather than on their actual beliefs or practical experience. Thus the responses to the latter question may reflect the "real" belief of housestaff that patients demand pain medication far in excess of their needs. If the above assumption were true, it would support Marks and Sachar's suspicion that medical personnel develop a puritannical-counter reaction to analgesic requests. It is difficult to determine whether this apparent distrust of the "pain patient" is the result of actual experience, e.g., drug addicts, or represents a psychological defense mechanism created for dealing with their sense of inadequacy and impotence in treating the patient in pain.

Discussion

With advances in chemotherapy and radiotherapy the life expectancies of patients with cancer has been extended. Antibiotics and palliative surgery have further increased the survival time of patients with malignant disease. As a consequence, medical personnel are faced with an increasing population of patients whose primary need is that of maintaining an optimal "quality of Life." In many terminal patients the chief complaint is that of persistent agonizing pain. Surgical and pharmacological techniques for the relief of pain are available. Yet, anyone who has been involved with the care of terminally ill patients in large teaching hospitals cannot help but be impressed by the suffering and misery endured by most patients and their families. Two questions are then raised: Are there available modalities for effective pain relief and if there are, why are not being employed?

In studies reported by Twycross (27) and Saunders (15) in England and Mount et al (18) in Canada, successful management of terminal patients in pain was accomplished through the use of comprehensive supportive care and judicious use of narcotic analgesics. By employing Bromptons mixture on a non "prn" basis, in initially moderately high doses, the majority of patients were kept free from pain without becoming stuporous or disoriented. In addition the frequently mentioned problems of tolerance and addiction were not encountered.

Why then have the strategies outlined above not been implemented more widely? Marks and Sachar (1) found that two general areas of misinformation contributed to physicians undermedicating patients in pain. First, physicians lacked an understanding of addiction in general overestimating the risks and dangers of addiction in the "medical" setting.

The aim of the present study was to further investigate the knowledge, attitudes and experience of medical personnel in various specialities engaged in the management of terminal patients, particularly terminal patients in pain.

The responses to questions on basic pharmacology were revealing. A variety of misconceptions regarding analgesics and their actions were found. These misunderstandings or misconceptions concerned the relative safety and efficacy of different analgesics, their site of action, duration of action, bioavailability, toxicity, and potentially dangerous drug interactions. Responses to questions on addiction indicated a surprising ignorance of the relative severity of withdrawal from narcotics as compared to sedatives and barbiturates.

Although Neoplastic fellows were more knowledgeable than surgeons and nurses, all groups displayed an ignorance of more recent advances in the use of narcotics in managing the terminally ill. For example, a majority of the respondees were unaware of the value of using oral long acting medications on a non-prn basis, and of the relative disadvantages of demerol over the opiates. In several instances a specific therapeutic regimen was employed to produce a given result, however; the regimen employed would have produced just the opposite of the desired effect.

Most housestaff felt their knowledge of pain management was inadequate and relied primarily on fellow or senior housestaff for most decisions involving pain medications and secondarily on their undergraduate medical school training. When faced with a problem in medication choice, the majority of housestaff turned to either the PDR or senior housestaff rather than formal textbooks of pharmacology. When faced with a specific decision regarding drug choice, selection was based on familiarity with the drug and prior experience rather than on relative safety, addiction liability, etc.

The goals of the surgical housestaff in treating chronic pain were somewhat more conservative than those of the nurses or Neoplastic fellows. Further when asked the results of the Marks and Sachar (1) survey the majority of surgeons believed that patients were over rather than undermedicated. These findings are difficult to interpret but suggest a lack of insight into the nature of terminal illness as well as pain and its treatment, i.e., the need to eliminate the existence as well as the memory of pain.

The majority of all respondees agreed that "anxiety" played a major role in determining pain medication requirements, yet as discussed above, their approach to management, e.g., use of prn medication and failure to examine patients pre and post pain requests, suggested little understanding of the relationship between medication regimens and relief from pain related anxiety.

Conclusions

The terminally ill patient presents a myriad of medical, social and ethical problems. These problems are dealt with best in a facility (hospice) oriented specifically towards providing supportive and maintenance care. Teaching hospitals are oriented towards diagnosis, intervention, and disposition. The emphasis is on "working up" the interesting patients and caring for the acutely ill. In this milieu, the care of the terminal patient is haphazard and insensitive at best but in many instances exceedingly cruel and inhuman. The results of the present survey suggested that one factor contributing to the poor care afforded terminal patients, is the lack of understanding of the basic concepts of pain management. What is evident from the data is that little if any effort has been made to enlighten medical personnel to the fact that a terminal patient need not spend his last days either incoherent from misused medication or in excruciating pain. Thus, as long as terminal patients are cared for in teaching hospitals, some emphasis must be placed on re-educating physicians and nurses on the most fundamental aspects of analgesic pharmacology, eliminating the mystique and emotional reactions which surround the subject of narcotics. In addition some attempt must be made to end the myths which are perpetuated regarding drug addiction, physical dependence and tolerance. Finally, medical personnel should be encouraged to examine their prejudices and fears of death and the dying patient which interfere with the care they provide. No patient can be allowed to endure pain so severe that he wishes for death because a physician has failed to realize that adequate analgesia is possible.

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Student Section

Malnutrition and the Developing Fetus: An Investigation of the Effects of Riboflavin, B-12, and Folate Deficiencies during Pregnancy both on the Mother and Fetus

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Working in a large metropolitan hospital one cannot help but be impressed by the inadequate nutrition of the urban poor. This becomes especially apparent when one is dealing with a population of pregnant women. There is general awareness about the importance of iron and folate supplementation during pregnancy. However, riboflavin deficiency, which has been implicated as a possible cause of anemia in the mother (26, 29) and which has been shown to produce a clearly defined teratogenic effect on the fetus (6, 7, 8), is often neglected. Riboflavin deficiency is often thought of as an entity that does not occur in the United States. However, in the 1968-1970 ten-state nutrition survey it was found that "six percent of children under six years of age of low income groups, and three percent of those under six years of age of an upper income group had unacceptable riboflavin values (1).

In 1972, after the issuance of the above mentioned report, Sauberlich et al (2), studied riboflavin (vitamin B-2) nutritional status in a group of four hundred and thirty-one Tennessee high school students. Utilizing the technique of the glutathione reductase assay (described in their paper) they found that "eleven percent of the students were considered to have inadequate riboflavin intake." The incidence was higher among girls (16.0%) than boys (6.5%), with the highest incidence occurring among black girls (37.9%). Riboflavin supplementation of 5 mg/day for one week corrected the biochemically measurable deficiency.

Riboflavin is found primarily in milk and green leafy vegetables, as well as in meat and eggs. Cereals, grains and legumes are poor in B-2. It would seem reasonable that populations depending heavily on rice, beans and other carbohydrates would be at risk for developing riboflavin deficiency. In addition, this problem may be compounded by the relatively common occurrence of lactase deficiency in a large portion of the black community, which further reduces milk, and therefore riboflavin intake.

Riboflavin deficiency during pregnancy was first shown to produce a characteristic syndrome of abnormalities in the developing fetus by Warkany in 1944 (3). However the mechanisms whereby the teratogenic effects are pro-

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duced have not yet been elucidated. It has been postulated that a pure B-2 deficiency does not exist, and a review of the literature makes it clear that riboflavin alone cannot be said with certainty to produce the effects commonly attributed to it, as folic acid and B-12 also appear to be involved in the process. The present paper is an attempt to explore some of the current hypotheses concerning the effects of riboflavin deficiency during pregnancy on both the mother and the developing fetus. We will commence with a brief description of the mechanism of action and role of riboflavin in the body.

Absorption, transport, metabolism and utilization of riboflavin

Riboflavin is absorbed in the upper intestinal tract, however the method of intestinal transport is still unclear. Riboflavin is phosphorylated in the small intestine to flavin mononucleotide. The method of absorption of riboflavin is not yet completely elucidated; however, bile salts seem to facilitate the absorption of riboflavin and flavin mononucleotide (FMN) (4). It has also been noted by some investigators that food enhances the intestinal capacity for absorption of riboflavin (5).

The main function of riboflavin lies in its role as the precursor of the two flavin coenzymes, flavin mononucleotide, and flavin adenine dinucleotide (FAD). Riboflavin is converted to flavin mononucleotide by the action of flavokinase and ATP. Flavin adenine dinucleotide is formed from riboflavin by the action of flavin nucleotide phosphorylase on FMN. The flavin nucleotides FMN and FAD act as the prosthetic groups of the oxidation reduction enzymes known as the flavin-linked dehydrogenases. Functioning in electron transport are two of the most important flavin linked dehydrogenases, DPNH hydrogenase which catalyzes the transfer of electrons from DPNH to a unknown receptor, and succinate dehydrogenase, by means of which succinate is oxidized to fumerate. Another important flavin-linked enzyme is glutathione reductase, which allows reduction of oxidized glutathione to reduced glutathione, using DPNH as hydrogen donor. This is necessary for the recycling of DPNH-DPN and for facilitation of the first step in the pentose phosphate shunt, the main pathway for the breakdown of glucose by the red cell.

Riboflavin and the deficiency state: Animal studies

The syndrome described by Warkany (6, 7, 5, 8) which affected fetal rats of mothers that had been maintained on a riboflavin deficient diet several weeks prior to breeding was "shortness of the mandible, tibia, fibula, radius and ulna; fusion of ribs and sternal centers of ossification; syndactylism, brachydactylism, and cleft palate." Later studies, using supplementation with galactoflavin, a riboflavin antagonist, reported CNS lesions, eye lesions and hydrocephalus (9, 10, 11).

Since the deficiency syndrome includes malformation and shortening of the extremities, as well as cleft palate and growth stunting, it is of interest to pursue the connection between B-2 deficiency and synthesis of RNA, DNA and protein. The effects of riboflavin deficiency on RNA and DNA metabolism in the livers of laboratory rats have been studied by Chatterje (12). It was previously shown (13) that rats fed diets moderately low in protein (15%

casein) "showed a large excretion of riboflavin in the urine and were unable to retain riboflavin in their organs." The same investigators found an increased demand for riboflavin in rats fed high-protein, high-fat diets. However these results may simply reflect the increased fat content of the diet, as lipid metabolism is dependant on riboflavin dehydrogenation of fatty acids, and is impaired in riboflavin deficiency (14).

Chatterje has found that after a short period of deprivation (45 days), liver RNA and DNA were unaffected in riboflavin deprived rats. However, after a long period of deprivation (70 days), RNA and DNA concentration seem to be decreased.

Although a reduction in FAD may be an important contributing factor in the production of congenital abnormalities, its connection with these defects as well as the decrease in birthweight and the slower growth of the offspring of riboflavin-deprived mothers remains to be determined. There appear to be critical periods associated with riboflavin deficiency. Warkany (6) found that if riboflavin was administered to B-2 deficient pregnant rats before day thirteen of pregnancy, malformations of the young could be avoided. Riboflavin stores appear to become changed or decreased in deficient pregnant rats and fetuses around day fifteen of gestation (15). Miller has shown that on day fifteen of gestation, fetuses of galactoflavin (a riboflavin antagonist)-fed rats contained a greater proportion of their B-2 as free riboflavin and as FMN rather than as FAD. When maternal livers were examined, it was noted that the deficiency had caused a "rapid depletion in the riboflavin reserves of maternal liver; total riboflavin was quickly reduced to 64% of normal in livers of riboflavin deficient rats and to 51% of normal in galactoflavin fed rats." However, unlike the fetuses, FAD in maternal livers, although reduced, nevertheless constituted 93% of the total liver riboflavin.

Since FAD is utilized as a coenzyme in many reactions it seems logical that a depression in tissue FAD would also affect the apoenzymes, and, therefore, as has been proposed (15), specific end products of the action of certain enzymes would be missing which are essential for normal growth and tissue differentiation. There has been some work to suggest that in a riboflavin-deficiency-state, xanthine oxidase, succinate dehydrogenase, and TPN cytochrome reductase are deficient (4, 14, 16).

Because of the essential role of the flavins in the electron transport system, it has been postulated that this system is altered in the embryos of riboflavin-deficient dams. Asku et al (19) studied the activity of the succinic and DPNH oxidase systems in embryos of B-2 deficient, galactoflavin fed rats. He found the activity of both enzymes was significantly higher in control than in experimental animals. The fetuses examined, ranging in age from 12 to 16 days were also significantly smaller in size in the experimental group than the controls. Asku suggests that "galactoflavin per se is not an inhibitor of enzyme systems. It may be that galactoflavin produces an effect on the electron transport systems of fetal tissue by either hindering the FMN and FAD during synthesis of the enzymes or by being bound itself to the enzyme in place of the flavin coenzymes, thus producing an inactive enzyme." Although it could be argued that severe B-2 deficiency was produced by artificial means, i.e., galactoflavin, still this is a useful tool for the elucidation of the effects of severe B-2 deficiency on the developing fetus. It is interesting to note that according to the above data, the electron transport system, which is essential for producing the energy necessary for cellular reactions, is diminished from the 12th to the 16th day of gestation in the riboflavin-deficient fetal rat, a period described as being essential to organogenesis in the developing fetus (15). Another investigator in the field of riboflavin deficiency (17) noted that the fetuses of dams fed a riboflavin-deficient, galactoflavin-supplemented diet showed marked cellular necrosis in their upper extremities at fourteen and fifteen days, as well as a significantly lower total body protein content beginning on day thirteen. This may be an explanation, at least in part for the "critical period" previously described in this paper. As will be noted in the following section this same critical period before which supplementation must be instituted in order to produce healthy offspring exists during folate deficiency as well.

Interrelationships between riboflavin, B_{12} and folate:

Prenatal deficiencies of other vitamins such as vitamin A have been shown to produce their own distinct syndromes in the neonate. However, in 1956, Nelson et al (18) fed a folic acid-deficient diet supplemented with a folic acid antagonist (X methyl PGA) to pregnant rats, and interestingly produced a syndrome of malformations strikingly similar to but more severe than that originally described by Warkany. This dietary regime was more detrimental to reproductive performance than riboflavin deficient galactoflavin-supplemented diets. Instituting the folate antagonist as late as seven to nine days post-breeding resulted in 100% fetal resorptions. All of the young produced by dams fed a folate deficient, folate antagonist supplemented diet from days ten to twenty-one exhibited at least some of the following abnormalities: edema, anemia, deformed bones, absence of certain ossification centers, visceral abnormalities, cleft palate, retardation in facial development, brachydactylism or syndactylism, short or curved tails. What was also striking was the similarity of timing in producing these effects to that noted with riboflavin deficiency. If the folate antagonist was begun on day 12 of gestation as opposed to day 11, the incidence of malformation in the young was decreased from 95% to 65%, the severity of the malformation also being reduced. Warkany in 1942 (6) designated the critical period for riboflavin supplementation as being between days thirteen and fourteen. However, the critical period designated by Warkany and that indicated by Nelson's results differ by only one day when it is taken into account that Warkany designated the day of finding a sperm positive vaginal smear as day one while Nelson designated it as day zero.

In 1959, Donaldson demonstrated for the first time that FAD was necessary for folic acid metabolism. His results showed that FAD is necessary for the first stage of citrovorum factor (folinic acid) synthesis. Citrovorum factor appears to be the main storage form of folic acid in the tissues of both riboflavin deficient and control rats (15). The role of folic acid in B_2 deficiency is interesting in view of the low birthweight and malformations of the fetuses, as well as the failure of older animals to gain weight on a B_2 deficient diet, for it is well recognized that "the most conspicuous biochemical symptom of folic acid deficiency is the inability to synthesize purines and the pyrimidine thymine" (19).

Bovina et al (20) postulated that the teratogenic effects of riboflavin and folic acid deficiencies were the result of "a common biochemical lesion, such as tissue depletion of folate coenzymes." When he placed male weanling rats on a riboflavin deficient diet, he found that in addition to a decrease in FAD, free riboflavin, and FMN, that the B-2 deficiency had affected the synthesis of tetrahydrofolate dehydrogenase and that the enzymatic activity which converts folate to tetrahydrofolate was markedly reduced.

Others have put forth further evidence that folic acid metabolism is impaired in riboflavin deficiency (21). This includes a marked decrease in N^5 methyltetrahydrofolate transferase activity. Further work by these same investigators has shown an accumulation of N^{10} formyltetrahydrofolate and tetrahydrofolate in the liver of deficient rats, which may be a consequence of the above. Other work has shown an increased excretion of labelled folic acid in riboflavin deficient animals.

An additional complicating variable in the relationship between riboflavin and folic acid is the complex interrelationship between riboflavin, folic acid and B-12. Grainger et al (12) observed eye lesions as well as hydrocephalus and skeletal abnormalities in the offspring of riboflavin deficient dams. The addition of B-12 relieved the eye lesions and hydrocephalus but not the skeletal abnormalities. What is more interesting however, is that the addition of riboflavin alone without B-12 supplementation did not reduce the incidence of skeletal abnormalities.

Many of the skeletal abnormalities commonly observed appear to be the result of faulty ossification. When alkaline phosphatase activity in the tibias of newborn rats was studied by Grainger in 1954 (11) riboflavin deficiency appeared to decrease the alkaline phosphatase activity in rat fetuses to 50% of normal values, while B-12 deficiency decreased the activity by 20%.

DeCourcy (22) in 1974, studied the electrophoresis of alkaline phosphatase in teratogenic riboflavin deficiency on both the whole rat fetus, chorioallantoic placenta, and visceral yolk sac from day thirteen to twenty of gestation. In this study, LDH levels of fetal organs were also followed to quantitate effects of maternal B_2 deficiency on placenta and fetus. It was found that B_2 deficiency delayed the appearance of isoenzymes of alkaline phosphatase in the whole fetus and of LDH in the fetal kidneys, suggesting "a similar delay in the course of metabolic differentiation of the skeletal and fetal tissues."

The above data would suggest that the production of skeletal abnormalities is not a simple case of riboflavin deficiency alone, but a result of the interaction between riboflavin, B_{12}, and possibly, protein.

What can be gathered from the animal literature, then, is that the effects of riboflavin deficiency on the developing fetus appear to result from an insufficient amount of FAD present for the developing fetus. As a consequence of this the apoenzymes dependent on the flavin coenzymes are affected. In particular, the electron transport system appears to be altered during what appears to be a critical period for fetal development. The deficiency syndrome may further be complicated by the absence of the other vitamins, particularly folic acid and B_{12}.

Riboflavin deficiency in the human

For many years the problem of investigation of riboflavin deficiency in humans was hindered by the lack of a simple and reliable clinical test of blood riboflavin levels which could be applied to field studies. However, in 1970 Glatzle et al (23) developed an assay for red blood cell glutathione reductase, an FAD-dependent enzyme, which could be performed on 2 ml of venous blood.

In riboflavin deficiency in humans, early clinical symptoms include angular stomatitis, cheilosis, and sore throat. Later, skin and eye symptoms, i.e., seborrheic dermatitis and glossitis, and photophobia, may occur. Late stages of the deficiency include neuropathy and mild anemia.

The true incidence of riboflavin deficiency in the U.S. is not known, although a correlation between riboflavin intake and family income has been found (1). Likewise, increased requirements for B_2 in pregnancy have not been systematically studied. Iyengar (24) in 1973 reported that in India, angular stomatitis and glossitis were particularly common findings among pregnant women. She hypothesized that these oral lesions may have originated with a deficiency of conversion of pyridoxine to pyridoxal phosphate as a consequence of riboflavin deficiency. Another interesting paper from India (25) reports a significant difference in the erythrocyte glutathione reductase levels in women using oral contraceptives (unspecified type) and controls. This is especially important in light of the fact that these women will probably at a later date decide to have children. The general adverse effect of oral contraceptives on B_2 nutrition in population groups with a low supply of this vitamin must still be investigated, especially in those populations with poor vitamin nutrition and a high prevalence of G-6-PD deficiency. Certain populations of American blacks fall into this high risk category.

The work that has been done on actual riboflavin deficiency in pregnancy in the US is very sparse, and not always very well done. Weber et al (26) in a discussion of the benefits of the glutathione reductase assay, refers to some intriguing, but unfortunately unpublished work by S. Heller and R.M. Salkeld. These investigators found that in 25% of pregnant women studied in the first trimester (increasing to 40% at term) there appeared to be a marginal deficit of riboflavin, as measured by the glutathione reductase assay. Unfortunately the population group was not further defined. In another unpublished study these authors "observed a higher incidence of low hemoglobin levels in blood when the total blood riboflavin levels were decreased. . . . The blood hemoglobin levels and values for packed cell volume correlated positively with the levels of total B_2 in blood."

The effects of B_2 deficiency on maternal hemoglobin are significant in light of the anemia of pregnancy. It is possible that giving folate and iron to anemic mothers who have generally poor eating habits anyway may not be entirely adequate. There is only one model for human riboflavin deficiency (27) in which the effects of riboflavin deficiency on hemoglobin concentration has been studied. These are patients with malignancies, in whom it was hoped that a riboflavin deficiency might arrest tumor growth. Alfrey et al (28) studied the effects of riboflavin deficiency in these patients and found the first hematologic change to be a decrease in reticulocyte count and a fall in hemoglobin concentration ranging from 3 to 9.7 gm/100ml. The red cells however remained normochromic normocytic. Administration of B_2 resulted in a reticulocytosis along with a significant increase in hemoglobin concentration. The authors concluded that "the anemia of riboflavin deficiency appears to be a type of chronic erythrocytic hypoplasia."

H.C. Clarke, an obstetrician-gynecologist on the staff of SUNY in Buffalo (29) has investigated the mean corpuscular riboflavin concentration (MCRC) in the blood of 37 anemic pregnant women, with hemoglobin < 12 gm, hematocrit < 36, "mainly hypochromic microcytic type." He looked at their hemoglobin, hematocrit, MCRC, and that of their cord blood, at term. The women were divided into three groups: one third were given supplemental iron and folate during their last trimester, one group was given iron, folate and B_2 and one group was composed of women who did not take their prescribed vitamins during pregnancy. No significant difference in hemoglobin or hematocrit was found in the cord blood of the neonates term. However, it was found that 80% of both maternal and cord blood, in the mother given iron and folate but not B_2, showed below normal values for MCRC; while only 10% of bloods in the other two groups had values below normal. These differences were significant at the .001 level. The authors feel that "this may reflect a rapid increase in red cell mass in the presence of depleted stores and low intake of riboflavin . . . lower maternal blood riboflavin values are associated with corresponding lower fetal values." They conclude that since congenital abnormalities have long been associated with riboflavin deficiency during pregnancy in animals, "it seems advisable that prenatal therapy of anemia include riboflavin."

The mechanism of transport of riboflavin between mother and child has not yet been satisfactorily elucidated. Lust (30) indicated that in humans, fetal (cord) blood shows a higher percentage of total riboflavin than maternal blood. Fetal blood appears to contain about four times more riboflavin than that of the mother, but about one half the amount of FAD. However an analysis of the placenta revealed that 95% of placental riboflavin was present as FAD. The authors suggest that neither free riboflavin nor FAD can easily cross the placenta, and furthermore that the placenta transfers riboflavin from maternal to fetal blood by taking in riboflavin from the maternal blood as FAD and splitting the FAD and secreting the free riboflavin into the fetal blood. The fetus would then presumably synthesize its own FAD from riboflavin. Perhaps in a deficient state, it is this method of breakdown of riboflavin and resynthesis of FAD by the fetus which is impaired.

Cooperman et al (31) used the glutathione reductase assay to apply to the pregnant woman and the newborn. He found that the glutathione reductase content of the erythrocytes of the newborn was higher than that of the mother.

In addition he noted that "In the pregnant woman, the major part of circulating riboflavin is in the form of FAD whereas that in the cord blood is free B-2 owing to enzymatic degradation of FAD in the placenta."

Clarke (32) measured whole blood riboflavin levels using his MCRC technique. He found that when mothers were given riboflavin during delivery, a rise in the fetal MCRC was higher than that of the mother in all but two of twenty cases studied. He suggests that placental insufficiency or insufficient riboflavin reserves may serve as an explanation in these two cases.

Following his work on maternal-fetal riboflavin levels in 1973 using the glutathione reductase method, Lopez et al (33) decided to study the riboflavin nutrition of a group of New York City school children. His results are suggestive that more work needs to be done in this field, for 11% of the children were found to have biochemical evidence of riboflavin deficiency. These data, taken in conjunction with the ten-state nutrition survey and the Tennessee study mentioned at the commencement of this paper, point the way for more research in this area. There may perhaps come a time when B-2 levels are measured in high risk pregnant women as iron and folate are now.

Summary and Conclusion

As far back as 1942, Warkany and his coworkers demonstrated a teratogenic effect of riboflavin deficiency on rat fetuses. Riboflavin, as the precursor of the two flavin coenzymes FMN and FAD, is necessary for many important enzymatic reactions in intermediary metabolism. What can be concluded from the animal literature is that the effects of riboflavin deficiency on the developing fetus appear to result from an insufficient amount of FAD. As a consequence of this the apoenzymes dependent on the flavin coenzymes are affected. In particular the electron transport system appears to be altered during what may be a critical period for fetal development. The deficiency syndrome may further be complicated by the absence of other vitamins, particularly folic acid and B-12.

The human syndrome of riboflavin deficiency includes characteristic lesions of the lips, fissures at the angles of the mouth (cheilosis), localized seborrheic dermatitis of the face, and glossitis. Riboflavin deficiency, however, is seldom seen as an isolated finding without other nutritional deficiencies as well.

Until recently there were no biochemical tools available for studying riboflavin deficiency among large population groups. However, with the advent of these methods (23) several important findings have emerged.

National nutrition surveys (1) have shown that "six percent of children under six years of age of low income groups, and 3% of those under six years of age of an upper income group had unacceptable riboflavin values."

In 1972, eleven percent of a group of 431 Tennessee high school students was found to be deficient in riboflavin (2). In 1975, a study on a group of school children from families of low socioeconomic status, found that 11% of these children had biochemical evidence of riboflavin deficiency (33). The ramifications of these findings are as yet unclear. It may be that pregnancy as a stress may exacerbate an already marginal riboflavin deficiency (24). One study reports that in selected populations as many as 25% of pregnant women in the first trimester and 40% of women at term may exhibit a marginal deficit of riboflavin, as measured by the glutathione reductase assay (26). However, no one has yet looked at the effect of pregnancy on riboflavin levels of young pregnant women who were found to be deficient as school girls. The importance of this lies in the fact that biochemical riboflavin deficiency may contribute to the anemia of pregnancy. It has been found that both reticulocyte count and red cell hemoglobin concentration fall when B-2 deficiency is induced experimentally in tumor patients. Some investigators (26) have observed that during pregnancy blood hemoglobin and packed cell volume correlate positively with the levels of total blood riboflavin, and low mean corpuscular riboflavin concentration has been described in groups of anemic pregnant women (29).

Although riboflavin deficiency during pregnancy has been shown to produce teratogenic effects on the rat fetus this has never been described in humans. Total deprivation of not only riboflavin but also folate and B-12 as well for an undetermined period of time would probably be necessary to produce such a syndrome. However, low maternal riboflavin levels have been associated with lower fetal values, and it has been hypothesized that in a deficient state the breakdown of riboflavin by the placenta and resynthesis into FAD by the fetus may be impaired.

Only enough work has been done in this field to give one a glimpse of what still is left to discover. However, it is certain that a syndrome of riboflavin deficiency can be produced in the animal model, and that biochemical riboflavin deficiency does exist in the United States, in school children and pregnant women. What this means in terms of long-term outcome for the fetus, as well as its significance in the anemia of pregnancy remains to be seen.

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Foreword

This issue of the Journal, dedicated to primary care, is an expression by a large urban medical center of its search to find a compatible relationship with primary care. Like most medical centers in a densely urban environment, Mount Sinai's clinics and emergency room serve a large constituency that has poor access to the private care system. The size of the constituency is a bequest of neighborhood-based practitioners who have long since gone. And like most urban medical centers, a recounting of an otherwise broad spectrum of institutional achievement would not include a special emphasis in training and research in the field of primary care.

Although Mount Sinai's faculty members have been involved in an enduring partnership with the people of East Harlem, in the development of their own health-related facilities, the intramural resolution of primary care as a separate discipline remains elusive. We have progressed to an understanding of primary care to be general medical care and that such care can best be demonstrated in a setting which bears little resemblance to a general medical clinic on a Monday morning.

We now turn to our consultant-contributors for their advice.

Dr. Edward Pellegrino reminds us that in the tradition of medicine we are dedicated to meeting the needs of the sick, and that "the case for primary care as an obligation of society is derived from the special vulnerability and the universal fact of illness. This vulnerability generates a need, which takes on the substance of a relative right because of the promises inherent in our social and political structures."

To quote our ethicist-consultant further: "We have, in a sense, all made a set of mutual promises that we will guarantee to each other a certain kind of society, one which is sensitive to, and secures those things closest to our needs as humans. We would break our communal promise, tell a communal lie, and live an inauthentic social life if we neglected to exert every effort to assure the minimum security of access to primary care wherever it is needed."

Evidence is in hand that equity of access to medical care has been achieved for broad segments of the US society. The gap in the average number of visits per year made by whites and blacks has been closed but can we say anything more? Long waits, broken appointments, a low probability of seeing the same physician, the emergency room and multiple clinics serving as surrogate for a primary care physician—or for the former movie house, its marquee emblazoned with announcements of all kinds of services inside—constitute a composite caricature of primary care for the Medicaid-card holder in the urban environment.

David Banta and Robert Graham, physicians dedicated to the public's good at HEW, tell us that gaps in general medical care in the United States have not escaped federal attention. Within the past 15 years the federal thrust has been directed first to increasing the availability of neighborhood-based services for the poor and most recently to improvements in the organization of medical practice and in enriching the supply of primary care physicians. As the abuse begets the law, incentives, poorly received, beget regulation—no less true when applied to medical services than to other human services.

Still on general issues, Robert Kalinowski shares with us a personal perspective gained from several years of promoting and overseeing new training programs in primary care.

Featherstone and Petersdorf present a convincing case for the general internist as the primary care provider for adults but indicate that general internists will not be trained in sufficient numbers without investments in new training programs and in reorganizing and refitting "the decrepit clinics that are the hallmark of general teaching hospitals." These authors cite the need to develop faculty that will teach and make scholarly inquiry in primary care—and share in the academic reward system.

Case histories of primary care—in a teaching hospital (Delbanco and Parker), in a large New York City municipal hospital (Stewart) and in an outstanding prepaid group practice (Watkins)—follow. Delbanco and Parker give chapter and verse to guide all who would venture to establish a primary care practice unit within a tertiary care center. On the opposite coast, the superb organization of the Group Health Cooperative of Puget Sound provides a stark contrast to daily struggles with the chaotic organization of New York City's municipal hospitals.

Our issue would not be complete without drawing attention to research opportunities in primary care (Williams and Brook), for it is the research that will establish primary care, in the academic environment, as a discipline. We finish our issue with the valuable perspective on the efforts of developing countries, with but a faction of our resources, to cope.

We acknowledge with gratitude the contribution of our consultants. Their offerings fulfill precisely the editors' objectives to discuss primary care at a second-generation level. Yesterday's issues related to defining primary care, to identifying primary care providers individually, in teams, or by specialty. The public perception of a shortage in primary care is now institutionalized in federal legislation.

The challenge to academic institutions is to upgrade the manner in which they teach, demonstrate, and gain new knowledge in the provision of primary care. Primary care, which people most often receive in a lifetime, should have as its natural habitat the office of a generalist in a community. But the ecology has been disturbed and, especially in the inner city, the multitudes look to the teaching hospital for their ambulatory care. How we at The Mount Sinai Medical Center can start to define primary care, in operational terms, as a discipline, is the issue at hand.

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The Social Ethics of Primary Care: The Relationship between a Human Need and an Obligation of Society

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Introduction

In primary care, as in all other forms of care, the moral and ethical issues are situated in a complex matrix of reciprocal obligations which simultaneously bind professionals, patients, and society. Some of these obligations are common to all forms of care, while others are modified in different ways specific to each form of care.

This essay examines only one of the questions in this complicated matrix: Is the human need for primary care of such a nature that it implies some obligation on the part of the health professions and society to make it universally accessible? Is there a moral center to primary care, or is it morally neutral? If there is an obligation of society with respect to primary care, is it absolute or relative? If relative, under what specific conditions is the obligation binding?

By delimiting the question thus, it is not meant to demean the importance of many other ethical issues in primary care. It is justified by reasons of space limitation, but especially by the urgency of the questions, and the political, legal, and economic implications of the answer we give to it.

This paper argues that the need for primary care is a universal human need, that it imposes a claim on society and the professions, and that the claim is relative not absolute, but nonetheless a strong one in a democratic, affluent, technologically capable society like ours.

This proposition will be developed in three steps: the first locates the moral center of primary care; the second defines in what sense it might be considered a right or obligation; and the third outlines the potential conflicts between such an obligation and others already binding on health professions and society.

The Moral Center of Primary Care

Wherein lies the source of a specific claim, right, or obligation with respect to primary care? To answer this question we need some operational definition of primary care. The admirable one recently advanced by a committee of the Institute of Medicine (IOM) can, in part, serve this function. This definition is more a descriptive essay then a strict definition but it should help to counter the laxity and multiplicity of existing definitions and make discussions and research studies more comparable (1).

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Nonetheless, even this admirable statement requires some modification and expansion for purposes of this essay. It sets forth the necessary conditions for optimal primary care very well, but not the sufficient conditions. It lacks precision in distinguishing primary care and especially its first-contact component from other forms of care which share with it the same characteristics. If we are to find something specifically moral in primary care we must locate this distinction more clearly.

The IOM definition enumerates five characteristics of true primary care: accessibility, comprehensiveness, coordination, continuity, accountability. They constitute primary care regardless of the specialty of the provider. The committee avers further that primary care must be rendered by a team and that it can be taught only in settings which exemplify these standards.

These characteristics are certainly qualifications necessary to optimal primary care, but they also qualify optimal care in any branch of medicine no matter how narrow. If every physician adhered to them, the whole of medical care would assuredly be improved. But the major deficiency which has generated so much of the public interest in accessibility to primary care would not necessarily be remedied. That interest centers in the mundane but ubiquitous human need for access to first-contact care, readily, efficiently, considerately, and competently ministered wherever one lives or is visiting in this country.

First contact care is, of course, not the whole of primary care as the IOM definition makes clear. It is, however, the part of the primary care spectrum that, unfortunately can be most easily neglected, even if physicians follow the IOM prescription within their own particular specialties. Even the so-called primary care specialties sidestep it all too eagerly in favor of what they consider more sophisticated models of care. Each specialty circumscribes primary care with its own restrictions: general internists emphasize personal care for adults; pediatricians for children; gynecologists for women. To care for the family they must form a troika. Family medicine comes closest, but it too is showing a tendency to retreat from high volume first contact care to the more sedate forms of low volume care for families.

Quality first-contact care cannot result from the fortuitous convergence of the partial efforts of the several specialties—even the primary care specialties. What is needed is unequivocal dedication to a system of care, geographically and temporally accessible at all times, and designed to respond to felt needs of medical assistance. Need must be interpreted, at least at the time of contact, broadly enough to embrace what the *patient* perceives as a "need," not the physician.

Those who presume to provide this kind of care must be willing to meet the patient on his own terms, by his/her definition of an "emergency" and to provide medical "assistance." "Assistance" means several things in first-contact care—specific treatment for curable disorders, to be sure. But the bulk of what is required is the capacity, humanely and competently, to respond to the human need for help with ills, most of which are self-limited or irremediable by specific treatment, but calling for counseling, symptomatic relief, reassurance, or education. Throughout, there must also be assurance that the simple will be separated from the serious and referred expeditiously to the appropriate level of care and that the patient will be assisted in threading his/her way through the seemingly perverse, and insuperable obstacles of referrals, institutions, and procedures which obstruct the patient's progress to attention.

From the public point of view, what is wanted is the personal security of medical advice and assistance nearby, vested in some identifiable place and some person with whom and to whom the anxiety of a medical event can be shared, transferred, or discussed. The universality and intensely human quality of this need are obvious even in seemingly trivial matters to anyone who has ever played a role in first-contact care, or who has experienced the fact of illness. Even the critics of too much medical care, and those who make policy decisions—the economists, legislators, planners, and physicians—rapidly become advocates when they or their families find themselves in need in the circumstance of illness.

This is not to gainsay the value and necessity of the more comprehensive components of primary care, the preventive and educational aspects, and the continuity lauded by the IOM definition. But the moral center of primary care, that segment which generates a moral claim, and leads inevitably in our kind of society to discussions of "rights" and obligations is first-contact care. This is the moral fulcrum on which all rights and obligations in health care ultimately must balance. It is the highest priority entry point for all of us as persons without which further assessments of rights cannot proceed.

Primary Care as a Moral Issue. Moral obligations arise whenever some right exists, that is, wherever a person holds a strong claim on another or on society. Obligations can also arise as the result of some act or declaration by a person or by society which generates an expectation or promise that something will be done or given. Ethics is a branch of philosophy, one function of which is systematically to analyze, define, and justify rights and obligations, as well as to identify the principles which underlie them and how conflicts among them may be resolved.

The philosophy of rights is a complex subject and we cannot engage it here. It suffices to say that the concept of rights is a fairly recent one, deriving from John Locke and the seventeenth-century concern for some protection against absolutist government. We have since come to regard some rights as absolute or nearly absolute, like the rights to life, liberty, justice, freedom of expression, and self-determination. This is because we regard these rights as intrinsic to being fully human, and because they are fundamental to many other more relative rights. They are restricted under only the most stringent conditions, usually only when their exercise by one segment of society limits the exercise of similar or other rights by others. Moreover, though we are all possessed of these rights we need not exercise them always, else social intercourse would be well nigh impossible.

Other "rights" are more clearly relative, since they are owed only when certain conditions give them substance and reality. If, for example, a government declares that education will be provided for all, or that a vaccine will be distributed free, then all citizens would have an equal claim. This claim is relative not absolute because it would be meaningless if there were no teachers or no vaccines. The right in these cases might by common consent be set aside to achieve some other human good: food, jobs, or housing.

In what sense may primary care be considered a right in our society and in our times? This is a limited question, but it is prior to the larger one of a right or guaranty to health care, or to the even more expansive right to health itself. The complexities and the conflicts of values in all these questions are not to be minimized and they present formidable obstacles, especially in a time of economic constraint (2). They are, despite this, unavoidable in any attempt at designing a socially just health care system. The possibility of a right to primary health care and to the first-contact component is a good point of engagement for all the larger issues as well.

The remainder of this essay argues that primary care is a relative right in our times and our society and that it takes on substance because of the expectations and promise such a society implies.

All rights of any substance are based in some common fact specific to human existence. A right or claim to access to primary care could be based in the universality of human illness and the need all humans share for assistance in healing and being healed. Few events are more distressing and more a threat to our humanity than a medical event. When an illness occurs, it immediately pushes aside most other considerations; other needs become subservient to the need to be restored to the freedom of movement, decisionmaking, and independence we associate with health and the fullness of being human (3). In illness our bodies, or our symptoms, become the center of concern, and the source of anxiety about what will happen to us, and what we should do next.

To relieve that anxiety, to transfer it, and to know what is happening, is to begin the process of healing or adaptation essential to the reconstruction of the individual's existence. The precise degree of any person's need, the extent to which disability and discomfort can be tolerated or integrated into living are highly individual matters. But every person at some time or other will be in the state of illness and in some degree a subject of the need for first-contact primary care.

There are things more important than health, though not many. The claim to primary care is, therefore, relative and not absolute like the right to life, liberty, freedom of expression, or justice. Yet these anterior "absolute" rights cannot fully be exercised when a person is ill. An argument could be made that health, while its definition is highly personal, is a prior condition to the full exercise of most of our most basic human rights.

Though a relative right, primary care becomes something of a moral imperative in our times and in our society. We claim to be a civilized society, one which among other things is sensitive to the fullest expression of each person's humanity. We also claim to be a democratic society, one which promises equity of access to at least the minimum of things essential to a humane existence. That we do not deliver fully on the expectations we generate either in housing, jobs, nutrition, or health care does not excuse us from the obligations we incur by virtue of our declarations. As a society we "pro-fess" to be civilized, democratic, and humane, and this is enough to raise reasonable expectations, and is constantly a promise and an obligation we must fulfill if at all possible.

These expectations are further enhanced by the enormous expenditures both of public and private funds for health care services, and institutions, as well as the education of health professionals. The health professions justify public support by declaring that they act in the public interest, so do the bureaucrats, so do the insurors, and even the proprietary institutions—though they admit to doing so for a profit. The whole health care establishment implies that it is offering a human good. These declarations engender the expectation that the consumers' notions of the basic needs pertinent to that good will be given high priority. Judging from public and legislative concerns, first-contact care is high in that priority list, even if it is not with the providers.

These social expectations are much intensified by the peculiar place health occupies in our culture. Our technologic society promises ultimate control of all the distressing elements in human existence. It no longer accepts the will of God or violations of a taboo as adequate explanations for illness. Illness loses its meaning, and together with its unpredictability, creates a special anxiety known only to modern man. In no other age was medicine capable of suggesting the possibility of physical immortality as it does for so many people today. Moreover, as affluence increases, the tolerance for even minimal discomfort decreases. Medicine has become the means not only for control of the more dire prospects in illness but the guarantor of a life free of even the more trivial discomforts.

This overdependence on medicine can have dire economic consequences, as we are being steadily warned. We are exhorted to remember that health has no greater value than many other good things in life and that there must be a limit to the amount we spend on what seems to some observers to be a cult of health. But before our cultural anxieties can be reduced to more rational proportions their present reality must be confronted—and we must be as wary of undervaluing as overvaluing health and medical care.

Much depends upon whether we view medicine as useful only when it offers radical cure, or whether we see it, in addition, as a more widely useful mechanism for caring, coping with, and containing those ills for which there is no radical cure. Granted its notable failings in caring, medicine can, and does, in large part, provide human assistance in the existential distress of illness. This assistance is of variable worth to different people but we must not, therefore, conclude that its social utility for many others is inconsequential even in economic terms. Primary care, and especially its first-contact component, is especially pertinent in this respect.

The crucial question, then, in the social ethics of primary care is not whether it is an absolute human right. Rather, we must ask ourselves whether in a professedly democratic affluent society with an abundance of available medical resources, we can allow so fundamental and universal a human need to go unfulfilled. Primary care, within the explicit framework of the "here and now" of our society, can be considered a relative human right, and a very real and pressing one. In other cultures, and other times it might very well not be regarded as such.

Looked at in this way, primary care has more of the quality of an obligation incurred by all of us by our mutual declaration of the kind of society we profess to be than a strict legal right in the Lockean sense. Locke's view of right has an adversarial and coercive quality that could negate much of what the public seeks from its health care system. An ethic of obligations voluntarily assumed, even if implicitly, seems preferable to a legalistically framed assertion of an absolute right.

Implications of Primary Care as a Social Obligation: Potential Conflicts. To accept primary care as a relative right or obligation owed to citizens of a society such as ours has obvious far-reaching implications. We face the same knotty dilemmas posed by regarding health care in toto as a civil right. The social, economic, fiscal, political and ethical implications of guaranteeing health care have been amply examined in recent publications (4–8). These essays are mentioned to indicate that the few ethical dilemmas I shall select in the remaining pages of this essay must be placed in a much larger context. These complexities can be illustrated by two sectors of conflict in making primary care even a relative right: the conflict with other forms of care; and with other obligations imposed on providers.

Some difficult questions arise immediately if we take the view that primary care is even a relative right. Is it ethically justifiable to give it a higher priority than other needed forms of care? Primary care does not exist in isolation. To assure access to it will lead ineluctably to assuring access to all forms of care. Is it not more socially defensible to divert resources to prevention rather than to meeting primary care needs, so many of which do not require dramatic treatment? Alternatively, should not our resources go into the more complex technologies, or research? If the argument for primary care as a human need is valid, does it not apply with equal force to other forms of care?

A similar set of questions may be asked about the relationship of primary care to other human needs outside the realm of health. Are we not overinfatuated with health and medicine? Are not housing and nutrition, jobs and personal security just as essential, indeed, more essential to a satisfactory human existence? More to the point, are the deficiencies in these matters not more deleterious to health than the absence of primary care? Or, will easy access not mean more abuse, inefficiency, and overuse of medical services?

Another set of conflicts becomes obvious when we examine the impact on providers—health professionals and institutions. Perhaps, the most significant factor limiting access and availability of primary care services is the maldistribution by geography or specialty of health personnel, particularly physicians. The social and living conditions in poor, remote, underpopulated, or crowded city precincts force physicians and other health workers to concentrate in the suburbs. They now exercise another right our society guarantees: the right to live and practice where and how one pleases. Current efforts to ameliorate maldistribution have centered on incentives to induce recent graduates to serve voluntarily for some period in underserved areas. These measures seem unlikely to assure equity of access anywhere approaching that required to fulfill an obligation of society with respect to primary care.

Some have suggested that the time has come when the obligation to provide equity of access to primary care should override the obligation of society to allow freedom of professional self-determination by requiring all recent graduates to spend a period of service in an underserved area. This is seen as a way to offset the privilege of a medical education made possible only by partial public subsidization. Lacking this, should government itself provide the needed service wherever it is deficient?

The trend in the last two decades toward ever more detailed regulation of medical practice and education is also as slowly making primary care a civil right, de facto if not de jure. It has been unofficially proclaimed as such in political rhetoric, and clearly enunciated as a major goal of PL 93–641 (9). But coercion of health professionals, and the inevitable adversarial spirit it induces might well be self-defeating. Health care by coercion is almost certain to be less satisfying to both patient and physician than an obligation voluntarily assumed by an ethically sensitive profession.

After all, the health professions do make a "pro-fession"—a declaration and a claim that all their acts are ultimately performed in the public interest. Do not these "pro-fessions" create expectations, and impose a responsibility to make them authentic? Is there a corporate responsibility which binds on the whole profession? Are not all members of the health professions to some extent culpable if the aggregate of their efforts neglect a fundamental need (10)?

These are legitimate ethical questions and substance for a debate just beginning to become public. Ordering the priorities among conflicting obligations is a crucial enterprise of ethical discourse. Resolution of moral dilemmas turns finally on what we consider to be "good" for individuals and for society. That resolution is seriously hampered by our collective inability as yet to define the acceptable conditions of social justice. Without such principles, it is not possible to choose rationally among competing claims.

By examining carefully the case for primary health care as a relative right we may be able to clarify our stance on the somewhat more fundamental questions of ends and purposes for the health care system. In any case, those who examine or raise ethical questions have some obligation to offer some tentative way of resolving obligations in conflict with each other. With the intention of advancing the discussion, and avoiding apodictic pronouncements as carefully as possible, the following might be a reasonable order of priorities.

Primary health care, and specifically its first-contact component, seems the minimal health care claim a citizen may make on a society of the kind we live in. It takes precedence over other forms of care because of its universality, and its intensely human dimensions, and because it is the critical point of first entry into the entire system of health care. It is fundamentally a form of personal security, and one of the benefits which ought to follow on the formation of society. Following this would be access to treatments which can effect a radical cure or prevent occurrence of a disease entirely. Next would come the care and containment of established serious disease for which no radical cure is available; then, the more expensive, highly complex procedures of dubious or unproven benefit; and last, treatment for disorders with minimal disability, which though distressing, are not incapacitating, and need only symptomatic treatment or self-care.

A nation must determine how far down this list it will go given its resources, and the expectations its form of society engenders. Whether health is preferred to other human services will depend largely on how far down the list of health priorities one wants to go. Since sanitation, housing, nutrition, and environmental safety contribute to health, they might well take precedence over health care items lowest on the list.

No matter what priority a society assigns to health among other human services, it quickly goes to the top for any individual when he/she becomes ill. Society cannot refuse help to a person in the present who is suffering. The promises of prevention, the welfare of future generations, the value of better housing, or jobs, cannot substitute for the here and now view of the sick. There is an inescapable immediacy about the call for help of a sick person that overshadows all other more remote social needs no matter how important. Until first contact primary care is secure for all, the options are really limited.

Economists point out, quite correctly, that polls often show that Americans place health low on their priority lists. But they do not tell us what the priorities are for those who are already sick. The transition from wellness exercising the fullness of our humanity, to illness in which that humanity is compromised, is so profound that the priorities of the well are meaningless for the ill. There is considerable warrant, therefore, if not on grounds of economics, at least on grounds of the realities of human existence to place medical and health care ahead of many of the other competing good things and advanced society can provide.

It should be noted finally, that in this analysis, no new moral or ethical principles have been introduced. The case for primary care as an obligation of society is derived from the special vulnerability and the universal fact of illness. This vulnerability generates a need, which takes on the substance of a relative right because of the promises inherent in our social and political structures.

We have, in a sense, all made a set of mutual promises that we will guarantee to each other a certain kind of society, one which is sensitive to, and secures those things closest to our needs as humans. We would break our communal promise, tell a communal lie, and live an inauthentic social life if we neglected to exert every effort to assure the minimum security of access to primary care whenever it is needed. We need resort, therefore, only to the commonly accepted principles of promise keeping, truth-telling, and fairness which govern any morally sound relationship between persons and between society and persons.

This analysis of the way a specific human need gives rise to an obligation of society has applicability to other relationships in which humans are vulnerable—like the patient-physician, client-lawyer, student-teacher relationships. In the case of medicine, it can serve as a starting point for the reconstruction of professional ethics in the post-Hippocratic era (11, 12).

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Political and Legislative Influences on Primary Care*

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> *The simple truth is that if the Association of American Medical Colleges and the American Medical Association had taken the steps necessary to train a proper balance of physicians and to make an active effort to see that the underserved areas of this nation had doctors there would not now be the support in the Congress for direct intervention to achieve these goals. Senator Edward Kennedy, The New York Times, March 21, 1976.*

> *The Congress and the American people have been patient—we have waited for curricular changes, we have waited for the geographic imbalance to self-correct, we have waited for an expected upsurge in numbers of primary care physicians. We cannot wait much longer. The time is now to forge a more effective partnership between the Congress and the participants in medical education—medical schools and their students. We must—through new health manpower initiatives—reaffirm our commitment to one another—and to the better health of the American people. Congressman Paul Rogers, Speech to the Association of American Medical Colleges, Nov. 4, 1975.*

The role of politics in a democracy is to define the scope and nature of government's activities in society and to assure that the wants of the people are translated into the administrative policy of governmental units. Although this is an imperfect and highly idealized generalization, it does lay out a general hypothesis that can be tested by the specifics of some types of social change. In a government such as ours, there is a variety of legislative and administrative levels where the people's desires can be communicated. The possibilities for action, should there be sufficient political pressure, include social sanctions such as laws and administrative regulations that implement those laws, and incentives of a fiscal or privileged nature. Depending on the predominant political philosophy at a given time and the acuteness of the problems addressed, there may be interest in providing incentives and encouragement, or the focus may be on coercive or regulatory sanctions. Generally, however, it seems that one is predominant at one time, and then the pendulum will swing in the other direction.

Background

The perception of a problem of inadequate access to primary care services has been gradually evolving in the United States during the last 15 years. During the 1960s, attention to the problem focused on the poor, and a variety of programs, including the Medicare and Medicaid financing programs and the

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* The views expressed in this article are those of the authors and not necessarily those of the federal departments or agencies with which the authors work or are affiliated.

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Office of Economic Opportunity neighborhood health center program, were, developed to improve access for those unable to pay for medical services (1–6). However, with the escalation in the costs of health care during the 1970s, the problem has come to be perceived as more general. One observer of the scene comments: "From all socioeconomic levels and widely divergent political persuasions, complaints increased regarding the difficulty of finding a personal physician and developing a satisfactory professional rapport with him. The absence of readily accessible general practitioners and the difficulties people encountered in finding medical care outside a hospital during the evening, on Wednesday afternoons, and on weekends came to be regarded as serious problems, and demands that ambulatory care be improved have since continued to increase" (7).

This formulation gains support from several recent polls in which the public expressed concern about the costs of medical care, identified removing the cost obstacle as the most appropriate action for the federal government, and expressed declining faith in their ability to obtain good medical care (8). The groups showing the largest loss of confidence in the ability to get good medical care from 1971 to 1976 were the upper socioeconomic groups (9). The same poll reported that 30 percent of those polled in 1976 favored assigning new physicians to areas of need for two years and 28 percent favored building more medical schools.

We believe that these public and professional concerns about lack of access to primary care services during the last few years have been translated into pressures to create a variety of legislative and administrative initiatives.

In this paper we will attempt to examine superficially the evolution of legislative interests and action in the area of primary care services and manpower in the United States in the last 15 years. In the context of our introductory comments, we will describe how legislative involvement in primary care issues has shown a distinct evolutionary pattern during the last 10 to 15 years; and we will show that this pattern has been influenced by public perception of needs, as well as the developing understanding of the unique role that primary care services and manpower play in the delivery of medical care. We will first describe how early "undifferentiated" perceptions of need led to federal intervention at the levels of access facilitation and structural reorganization, while later interventions have been focused much more directly on the development and distribution of specifically trained primary care professionals. Because the majority of the targeted legislative primary care interventions has dealth specifically with manpower, either in its production or its distribution, this paper will carry a heavy emphasis on those issues. In a closing section, we will comment on some apparent successes and failures of these legislative initiatives, and will suggest some possible future directions.

Financing Policies (10)

The Medicare Program. The major result of this legislation has been summed up as follows: "One of the important lessons gained from recent government efforts to increase entitlement is that modifications of one aspect of the system (such as financing) without attention to the context in which change will be introduced results in enormous costs relative to the benefits" (11).

The Medicare program resulted from attention in the early 1960s to the special health and economic problems of the elderly. The aged were found to have more chronic illnesses than other groups, to use health care services more, and to incur higher medical care costs, while having lower incomes. The result of concern for this problems was passage of Title XVIII of the 1965 Social Security Amendments to provide a federal program of health insurance for the aged. The goal of the legislation was to reduce the financial barrier to access to health care, especially hospitalization. The legislation was not designed to influence the organization or nature of medical services. In fact, the legislation contained an explicit statement that it was intended to allow federal supervision or control over the practice of medicine or the way medical services were provided (Section 1801).

The effect of Medicare on access to primary care services is difficult to assess. Part B of Medicare, which covers ambulatory care services, is optional, although most Medicare enrollees do enroll. The immediate impact of Medicare was to lower the use of outpatient clinics by the elderly in favor of physicians' offices, but in the 1970s, visits to outpatient clinics replaced home and office visits. Higher cost-sharing imposed in the past several years has interfered with use of ambulatory services, so that higher income elderly people use more such services. Medicare also contributed to rising costs of medical care, which acted to curtail access, especially to outpatient care. Finally, aspects of the reimbursement under Medicare have provided incentives counter to increasing primary care services. Reimbursement to physicians is generally provided on a fee-for-service basis and is given up to a "reasonable" amount, meaning what is customary. Since fees are generally higher in urban areas, the incentives are for physicians to practice in those areas. Further, specialists are paid more than generalists for the same service. Finally, procedures are reimbursed at higher rates than such services as routine physical examinations, leading to a probable excess in medical and surgical procedures and discouraging primary care services.

The Medicaid Program. As in the case of the elderly, the 1960s saw rising concern about the lack of access of the poor to health care services. This concern led to the passage of Title XIX of the 1965 Social Security Act Amendments to establish a program to reduce financial barriers to access to health care for that group. As in the case of Medicare, the intent was only to develop a financing mechanism and not to alter the nature or distribution of medical care.

The Medicaid program is a state-administered program, with the federal treasury paying approximately 50 percent of its costs on average. A major problem with the program is its variabilities and inequities from state to state. States have frequently changed eligibility requirements as a mechanism to save money and have put restrictions on service benefits, physician reimbursements, and enrollment in innovative programs. These restrictions have hit particularly hard at the medically needy because of different determinations of income levels for eligibility depending on the state.

The result of the Medicaid program has been a significant increase in access to primary care for some of the poor. However, these benefits have not been distributed evenly among and within states. There have also been unintended side effects, including contributing to the rapid increase in the cost of medical care. A particular problem has been low fees that encourage provider-generated visits, inappropriate laboratory testing, fraud and abuse, and similar unnecessary costs.

Programs to Change the Organization of Medical Care

In the middle to late 1960s, as some of the early results of the Medicare and Medicaid programs were becoming visible, there was a growing consensus in the Congress that simply providing assistance in meeting health care costs would not be sufficient to balance the inequities of services available for some segments of the population, particularly the poor. In the "interventionist" mood of the latter days of the "Great Society," legislation was developed and passed that sought to provide new structures for delivery of a unified set of services to urban, inner city populations. Here, for the first time, federal recognization of the need for community-based, primary care services appeared, not only as a matter of "access," but also as a central element in the provision of a comprehensive set of health services and as a health maintenance stragegy.

Neighborhood Health Centers. Under the program of the Office of Economic Opportunity (OEO) in the 1960s, a network of neighborhood health centers was developed to serve the poor. Eventually, more than 100 such centers were developed, first under OEO funding and later by support from the Department of Health, Education and Welfare. As with many other "Great Society" programs, the initial promises were not met, and there have been difficulties maintaining even the limited number of centers.

For those served, the health centers have been quite effective in delivering comprehensive health and social services to the poor of certain areas. There seems little question that access to high quality primary care services has been enhanced in those areas.

Children and Youth Projects. Beginning in 1965, support was authorized for special projects to supply comprehensive care to low income children. By 1972, 76 grants had been awarded, to produce a potential eligible population of over 3 million, or about 21 percent of those potentially eligible in the nation. Actual registration in 1972 was only about 500,000, or about 16 percent of those eligible by age and location.

For those children served, the Children and Youth Projects have provided high quality primary care. However, increasing costs and decreasing interest in categorical community-based programs make significant growth in this approach unlikely.

Health Maintenance Organizations (HMO). The Health Maintenance Organization strategy was first presented in the Nixon Administration's 1971 health message. The result was the Health Maintenance Organization Act of 1973, whose purpose was to foster the development of organized systems of care to serve enrolled populations. The legislation provided loans and grants for developing HMOs and also provided that enrollment in a qualified HMO should be offered as a health-insurance option to all personnel in businesses employing at least 25 persons. Since most of the population has health insurance related to their place of employment, the latter provision could greatly increase the market for HMOs.

There is good evidence that HMOs can help solve problems of health services delivery. Comprehensive care is offered to all enrollees for a prepaid premium, in some case significantly improving access to primary care services. However, there is no suggestion that HMOs can solve all the problems of access and cost of the health care system.

Changes in Health Manpower Legislation

In recent years the focus of legislative interest on the part of the Congress (and increasingly, state legislatures) in attempting to improve access to primary care services has come to be the system by which we produce various types of health manpower. Federal Manpower Acts in 1971 and 1976 concentrated specifically on issues of training primary care health manpower, and on facilitating their practice location in underserved areas (12). To do this, the Congress has addressed itself legislatively to a series of issues related to the mechanisms by which health professionals are trained. Some of these legislative interventions have involved incentives for new activities (e.g., family practice residency training), while others have been quasi-regulatory (e.g., capitation with performance requirements and scholarship payback provisions). Since this Congressional interest on primary care manpower has become a keystone to the federal strategy of increasing available primary care services, some historical consideration of the development of our present medical education system and its possible "pressure points" that Congress seeks to influence is in order.

History of Medical Education. The present medical curriculum was largely developed in the early decades of this century following the Flexner report. At the turn of the century, there was a plethora of medical schools, most of them proprietarily owned and operated. An individual seeking to become a physician might or might not attend one of these schools and might or might not augment this experience with a period of apprenticeship to a practicing physician. However, major changes occurred, catalyzed by the Flexner Report of 1910. Large numbers of proprietary medical schools closed and the pattern of university-based undergraduate medical education prevalent today began to develop (13). Contemporaneous with this trend was the appearance in the early 1920s of a year of "internship." Since not all states required training past the M.D. degree for medical licensure, the pattern in the early 1930s was that a significant number of physicians entered practice directly from medical school, while the vast majority of those who had any "graduate training" did only one year of internship before entering practice. During that period, 70 to 80 percent of all practitioners and those entering practice were termed "general practitioners."

World War II accelerated a slow trend toward specialization in medicine. The US military service provided special incentive pay and personal perquisites in the 1940s to those who had specialty training. In the immediate postwar era, this perceived preference for specialists and specialty training was accentuated by targeted federal research in biomedical sciences and by the growth of medical center complexes surrounding medical schools. A superb research establishment and a great increase in biomedical knowledge resulted, but both factors fostered an educational system that emphasized specialization and basic and clinical research and deemphasized services, especially primary care.

Medical school faculty changed significantly in the post-World War II period. Whereas medical faculty until World War II were frequently part-time and thus retained an independent practice base away from the medical school, by the late 1950s and early 1960s almost all medical school faculty in the basic and clinical sciences were full-time in the medical center complex. Frequently they had little or no independent practice experience in their specialty. Simultaneously, the generalist physician role model began to disappear from medical schools.

In the 1960s, the trend towards specialization reached its height. During this period, it was assumed that any student of quality would pursue specialty training. There was essentially no specialty training in general practice, as it was perceived that the work of the general practitioner took no special preparation or skill. Markedly shrinking percentages of graduates of US medical schools entered general practice, with percentages under 10 percent of a graduating class being common (14). The result was a decline in the number of general practitioners, from 64 percent of all physicians in 1949 to only 24 percent in 1973 (15). Serious problems of specialty and geographic maldistribution also resulted (16).

Within the last 10 to 15 years, it has been the federal role in the support of health sciences education—particularly medicine—that has changed most dramatically. Until 1965 almost all federal contributions to schools of medicine were limited to support of defined research activities and to a lesser extent (pre-Medicare and Medicaid) patient care. In 1965, however, the first basic grants to medical schools (for construction) were approved by the US Congress, along with the initiation of federal aid to a variety of health science student loans. In 1968, when the original Health Professions Education Act was renewed and extended, the first appearance of capitation funds to schools of medicine (called at the time special improvement grants) occurred with a performance requirement of an increase in student numbers in the entering classes. Since that time, the general issue of capitation support to schools of medicine and other health professions schools has become a major public policy issue, involving the conflict at the interface between institutional and public interests. Increasingly, capitation grants are made with required quid pro quos, e.g., expanded enrollment, maintained nonfederal support, and specially defined programs of national need. Each time the legislation was renewed, new requirements were added and new programs addressed to improving the health manpower situation were developed.

Nursing schools were supported by institutional grants beginning in 1968, and the Nurse Training Act of 1971 had several similarities with the provisions for medical schools, including a capitation program. The 1971 Comprehensive Health Manpower Training Act authorized special support for training programs to fill the primary care gap, especially nurse practitioner and nurse-midwife programs. Nurse practitioner programs were also supported in legislation in 1975 and 1976.

Another manpower program began with the support in the 1971 Act for training programs for physicians assistants. That support has been renewed and extended.

The 1971 Act also provided special project grants to operate approved residency programs in family medicine and to provide stipends to residents being trained in such programs. The Academy of General Practice was created in 1947 to foster general practice. However, general practice was not a specialty and had little status. In 1969, residencies started in family medicine and family medicine was approved as a specialty. In 1972, the Academy changed its name to the American Academy of Family Physicians. By 1977, there were 321 residency programs in family medicine (17). There is little doubt that federal support was critical in this growth, although as will be discussed later, state support has also been important.

Two other programs were developed to encourage medical graduates to enter primary medical care careers. The National Health Service Corps, in which new medical schools graduates agree to spend at least one year in an underserved area for each year of scholarship assistance, was developed in 1970 and 1972 legislation. The 1971 Manpower Act also developed the Area Health Education Center (AHEC) program, following recommendations in the Carnegie Commission Report, *Higher Education and the Nation's Health* (18). There are presently 11 federally funded AHECs.

The effect of the programs and policies of the 1971 Manpower Act was mixed. Although the Act provided for a dramatic increase in the size of medical school entering classes, from 8,770 in 1962 to 15,600 in 1976, the growth in surgical and specialty medical training positions continued to keep pace. Entering first year graduate training positions in family medicine were 12 percent of the total in 1976, but were still inadequate to meet the demand on the part of graduating medical students (19). Although there was some early evidence of increasing primary care interest on the parts of internal medicine and pediatrics, substantial numbers of those entering these fields had plans to practice only within a subspecialty area after graduation. In addition, although nurse practitioners and physician assistants were trained in an increasing number of programs in the US during this time period, their numbers were still relatively small. On the whole, although the 1971 to 1976 period saw some hopeful signs of reversal of the trend away from primary medical care practice, both the public and the Congress continued to perceive a serious problem.

This led to the 1976 Health Professions Educational Assistance Act, which continued the AHEC program, the National Health Service Corps, nurse practitioner training programs, and support for family medicine training. A new loan program was established for the National Health Service Corps, requiring service in the Corps and providing loan forgiveness in return. Grants were authorized for the development of new medical schools emphasizing training in family medicine. Grants also were authorized to support training in general internal medicine and pediatrics. And most importantly, all medical schools are required, as a condition of capitation support, to have a specified percentage of filled first-year residency positions in direct or affiliated residency training programs in primary care. By fiscal year 1980, the percentage rises to 50 percent. The term "primary care" is functionally defined as general internal medicine, family medicine, or general pediatrics.

Thus, in recent years health manpower legislation has tended to become more regulatory in nature. As implied in the introduction, we believe that this trend will continue as long as a continuing problem is perceived.

History of State Legislation. Since the late 1960s, states have developed a variety of approached to improve access to primary care services for the populations within their borders. An early state action was a 1969 act that required a family practice department in all state medical schools in New York. Subsequently, California, Florida, Illinois, Kentucky, Ohio, and Tennessee either have required such departments or required the teaching of general or family medicine. By 1977, practically every state has taken some legislative action to affect medical schools or residency programs within its borders to improve primary care manpower (20). Most of these have been specific financial support for family medicine programs in undergraduate and graduate medical education. In some cases, the action has been confined to a resolution exhorting action from schools within the borders of the state. However, the trend is for increasing state involvement.

Discussion

In this paper we have reviewed the developing political awareness on the part of national and State legislatures of issues related to primary care. Because of length limitations, we have not been able to address federal initiatives such as those in the Veterans Administration and state initiatives that affect the organization and delivery of primary care services. However, the material presented demonstrates that basic problems of access to general medical services have led to a variety of legislative interventions, starting with the provision for financing for medical services, and working through the development of strategies that also address the organization and structure of practice and the numbers and types of health care practitioners.

One overriding problem in these legislative initiatives seems obvious: there has been no comprehensive strategy for improving access to primary care services. The various interventions that have been attempted thus far have little apparent relationship to each other. Changes in the financing system, for example, have occurred without reference to manpower development policies and have, in some cases, exacerbated some of the problems of maldistribution. Medical schools have produced increasing numbers of physicians under the stimulation of Congressional incentives and requirements, but largely without regard to the types of specialties selected by these students or the location of their practices.

It can be argued that such a fragmented, disarticulated approach to public policy issues is as typical of legislatures in a democracy as is their incrementalism. Clearly there have been public forces leading to political support for change, but the types of changes accomplished have been, at least initially, those perceived as being least disruptive of the present system. However, with this past as prologue, it is becoming increasingly clear that future legislative initiatives directed at improving the accessiblity and status of primary care services will have to address at least four major issues concurrently if the derivative strategy (or strategies) is to have a reasonable chance of success.

1. The production of medical manpower. Increasing attention must be given to the total proportion of medical graduates electing to enter graduate training in programs specifically oriented to the preparation of primary care practitioners. The influences of medical student selection and of medical school curricula on the eventual career decisions of medical students must be better elucidated, and those influences supportive of primary care practice may need specific support and legitimization.

2. Distribution of professionals in practice. Distribution of graduates of primary care residencies will need to be closely monitored and evaluated. Assurances must be provided that those areas of the country with the most critical need for access to primary care, i.e., rural and inner city America, do, indeed, receive a proportional number of those new graduates initiating practice.

3. Practice structure. Close examination must be given to the competing claims of various practice structures regarding cost and quality of care and patient acceptance. There will need to be better delineation of the relative strengths and weaknesses of various methods of payment, particularly fee-for-service versus salary or capitation (as in prepaid group practice). Additional attention and research must also be given to the impact of practice structure, e.g., solo, single specialty, mixed specialty, or innovative mixes of personnel.

4. Impact of reimbursement patterns on primary care services. There must be careful examination of the possible disincentives presently provided to the provision of primary care services, especially in rural areas, by existing fee structures. Careful attention must also be given in the development of any national health insurance plan to the rationale and incentives in these structures related to the practice of primary care medicine.

Summary

In this paper we have described the developmental history of legislative policies over the past 15 years designed to promote access to primary care services. We have also considered briefly some future issues that must be considered by policy makers in the development of importance of coordination of policies, while recognizing that there are natural patterns in the development of public policy in a democracy that lean toward an incremental approach. We do believe that the public continues to perceive a serious problem of access to primary care services and we anticipate that this perception will give future support to the development of legislative strategies that may emphasize "regulation" rather than incentives.

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Primary Care Training: Some Random Thoughts

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Significant and rapid changes in graduate American medical education are taking place that could affect the conduct of practice, and the shaping of future national health policy.

These changes are influenced and directed by governmental forces to 1) increase the number of physicians and other health professionals in training, and 2) to shift the emphasis from the growth of subspecialty training to primary care training. As a result of the former, it is estimated that the number of active physicians will increase from 348,960 to 559,820 in 1990, assuming the continued stimuli of public funds. In addition, the growth of physician extender programs will accelerate six-fold using conservative assumptions, so that 41,500 extenders will be available for work (Table I).

More recently, additional Congressional appropriations have been added to earlier state efforts to increase the number of primary care physicians in family practice, general internal medicine and pediatricians by increasing the number of residencies available in these specialties (Table II).

In the academic year of 1974, there were a total of 18,834 M.D.s in the first postgraduate year of training, compared to 11,080 in 1960. This represents a 70 percent increase.

It should be noted, however, that the actual counts and percent increases overstate the ultimate number of primary care specialists because increasing numbers of first-year internists and pediatricians later enter subspecialities. For example, based upon recent trends, about 9 percent of those who entered first-year residency training in internal medicine programs in 1973 were not in second-year programs in 1974. It is assumed that this 9 percent is made up of physicians who elect one year of training in primary care prior to beginning training in the surgical or other nonprimary care specialties—probably due to the abolition of the free-standing internship in 1975. Similarly, it is conservatively estimated by the AMA that another 25 percent of those completing at least one year of general internal medicine training will later enter the internal medicine subspecialties. The same phenomenon has occurred in pediatrics with about 8 percent of all the first-year residents in general pediatrics entering the pediatric subspecialties. Thus, the number who remain in primary care in internal medicine could be reduced to 3,107, and the number remaining in pediatrics to 1,655. Applying similar corrections to 1974 figures, the percent in primary care would be 32.5 percent as opposed to 41.0 percent as previously stated (1).

However, if obstetrics and gynecology are added to the federal assumptions, Ginzberg believes that we have already reached the 50/50 point in the Congressional mandate (2); that is, that the number of residencies, as described in the Health Professions Educational Assistance Act, in each training program shall be so constituted that 50 percent of all first year residencies be in "primary care" specialties by July 15, 1979. Quantitatively, one might be lulled into accepting these figures as pro forma evidence that the growth rate in medicine

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TABLE I

ACTIVE M.D.s BY MAJOR SPECIALTY GROUP:
Actual 1974; projected (Trend) 1975–1990[7]

Specialty group	1974	1975	1980	1985	1990
	Number of active M.D.'s				
Total	348,960	361,300	428,360	493,830	559,820
Primary care	133,590	138,280	176,440	216,760	257,730
Other medical specialties	18,480	19,600	24,240	28,990	33,610
Surgical specialties	98,670	101,370	111,610	121,640	131,300
Other specialties	98,230	102,050	116,090	126,570	137,190
	Percent distribution				
Total	100.0	100.0	100.0	100.0	100.0
Primary care	38.3	38.3	41.2	43.9	46.0
Other medical specialties	5.3	5.4	5.7	5.8	6.0
Surgical specialties	28.3	28.1	26.1	24.6	23.5
Other specialties	28.1	28.2	27.1	25.6	24.5

[7] See bibliography

PRESENT AND PROJECTED SUPPLY OF PHYSICIAN EXTENDERS (PHYSICIAN ASSISTANTS[7] *AND NURSE PRACTITIONERS) 1975, 1980, and 1990*

	1975	1980	1990		
			Basic	Low	High
TOTAL PHYSICIAN EXTENDER	7,640	18,840	41,550	29,040	57,590
Total Physician Assistants (PAs)	2,540	7,410	18,520	13,200	27,700
–Physician Assistants	2,100	6,550	16,640	11,790	26,440
–MEDEX	400	860	1,880	1,410	2,860
Total Nurse Practitioners (NPs)	5,100	11,430	23,030	15,840	29,890
–NP Certificate	3,800	8,270	15,680	11,140	20,210
–NP Masters	1,300	3,160	6,350	4,700	9,680

and pediatric training programs solves the problem of providing physicians who will practice in a mode that closely resembles the Charney-Alpert definition of primary care.

We know from past experience that this is not so—that merely increasing the numbers will not qualitatively change the practice patterns of physicians. Most of us do what we have been trained to do (radical breast surgery, coronary bypass, gastric freezing, etc.)

Since the number of physicians trained will increase at a predictable cost (now estimated at $1 billion per year), it is not surprising that the future costs to the GNP and society will also escalate.

"Both Canadian and American estimates point to the fact that the new addition of one physician adds approximately $250,000 to the annual operating cost of the health-care enterprise" (2). The growth may not be linear, since it has been suggested by some, that physicians, especially primary care physicians might place less emphasis on applying available technology and more on continuity and integration of patient care. Nonetheless, it is inevitable that

TABLE II

Trend data on number and percent distribution by specialty of first year residents,[1] *and comparison between first year positions offered and filled, 1960, 1968, and 1974*

Specialty	Total number and Percent Distribution of First Year Residents, 1960, 1968, and 1974						Percent Growth Between 1960 and 1974, and Between 1968 and 1974	
	1960		1968		1974			
	#	Percent	#	Percent	#	Percent	% Growth 1960–1974	% Growth 1968–1974
TOTAL	11,080	100.0	12,864	97.8	18,834	100.0	+ 70.0	+ 46.4
PRIMARY CARE	3,443	31.1	3,796	29.5	7,724	41.0	+124.3	+103.5
General Practice	364	3.3	258	2.0	162	.9	−124	− 37
Family Practice	—	—	—	—	1,199	6.3	—	—
Internal Medicine	2,193	19.8	2,589	20.1	4,553	24.2	+153	+114
Pediatrics	886	7.9	949	7.3	1,810	9.6	+104	+ 91
SURGICAL SPECIALTIES	4,274	38.6	4,475	34.8	5,852	31.1	+ 47.3	+ 23.1
General	2,122	19.1	2,394	86.1	2,639	14.0	+ 24	+ 10
Neurological	101	.9	119	.9	129	.7	+ 27	+ 8
Ophthalmology	288	2.6	418	3.2	504	2.7	+ 75	+ 21
Orthopedic	353	3.3	403	3.1	609	3.2	+ 72	+ 51
Otolaryngology	153	14.2	206	1.6	270	1.4	+ 76	+ 31
Plastic	47	.4	90	.7	184	.9	+298	+104
Thoracic	89	.8	137	1.1	147	.8	+ 65	+ 7
Colon & Rectal	—	—	6	.05	30	4.8	—	+500
Urology	204	1.8	222	1.7	310	1.6	+ 52	+ 40
Ob/Gyn	917	8.3	759	5.9	1,030	5.5	+ 12	+ 35
OTHER MEDICAL	102	.9	259	2.0	381	2.0	—	+ 4.7
Pediatric Allergy	—	—	39	.3	59	.3	—	+ 44
Pediatric Cardiology	—	—	54	.4	58	.3	—	+ 7
Dermatology	102	.9	166	1.3	264	1.4	+102	+ 63

more physicians, using more technology, will increase costs unless their attitude and training change, on the one hand; and the expectations of the public for immediate technologic miracles change, on the other hand.

Some, such as Ginzberg from Columbia, suggest a frontal assault upon the Congress and the bureaucracy, to convince them that more is not better, that technology harms when overutilized, that all people cannot have all things (2). As it stands now, no lucid statement has been put forth by American academic and practice leaders that feasible, and maybe less costly and safer, approaches are available to the American public in achieving a longer and more satisfying life. Perhaps the reticence comes about because of the fear that the critics will raise the spectre of monopoly and protectionism. The alternative is to do nothing and let the polyglot of federal and state programs continue and accelerate so that they will run up their engines into one final Armageddon of well-intentioned, but confusing and uncoordinated bureaucratic melange.

Convinced in 1972 by preliminary studies which indicated that medical students were opting for careers in primary care, and that physician extenders could contribute to the productivity of physicians, The Robert Wood Johnson Foundation initiated a program (4) to support institutions who were interested in developing a training program that:

1. provided for residency training in general internal medicine, general pediatrics, and obstetrics/gynecology.
2. provided continuity experiences in ambulatory settings designed to provide care for individuals and/or families on a regular, coordinated basis,
3. provided for training and/or association with nurse practitioners/PAs with residents, and
4. identified an administrative focus within the institution for coordinating the training of internists, pediatricians, ob/gyn and physician extenders.

The number of institutions prepared to launch such programs was obviously limited, both by past tradition and present reimbursement mechanisms. With partial support for faculty and stipends, a nucleus of eight institutions began training programs that were usually "tracked," but over time, developed a sense of integration into the whole of the residency program as traditional residents oversubscribed electives in primary care. Few "pure" programs evolved, since institutions and their departments were in various states of readiness. Over time, however, most of the criteria were met, with obstetrics/gynecology either reluctantly involved, or not at all. This may represent bias on the part of the grantor, and may not accurately reflect the true state of affairs, since ob/gyn is undergoing a reassessment of its place in the hierarchy of care. Surprisingly, and less obvious, was the posture of pediatrics—it either felt it was already in primary care, so why all the bother? or had an impression that pediatrics might not be viable as a primary care specialty, and should seek its place in the tertiary care orbit.

New ways of doing things, new infusions of money, caused some dislocation as vice-presidents, deans, chairmen, faculty and residents shifted priorities and rewards. A few individuals resigned or left for other assignments.

With the passage of the Health Professions Educational Assistance Act of

1976 (PL 94-484), money was earmarked for programs in family practice, general internal medicine, and general pediatrics. A total of $15 million is appropriated in Fiscal Year 1977 for primary care, including undergraduate and graduate training, and an estimated $15 million is allocated for FY 1978. Both foundation and federal funding (with the potential for state funding developing) will launch programs to recruit faculty and residents into a lifetime career of primary care. I do not believe we can take refuge in the increased number of generalists that will be produced by these programs, or assume that the professional and bureaucratic solution is the answer to patient primary care requirements. The time is now to start asking questions:

1. Will projected national health policy take into account the wants of patients for the type of practice they prefer?
2. Will the nation's medical schools and training hospitals accommodate their training programs to produce doctors who will provide a service that the patient wants and can pay for?
3. Of all the things we do to patients, what do we do that works, and what doesn't work? What helps and what hurts?
4. What is of minimal benefit with potential harm to present patients and future generations?

And finally, what of the conventional wisdom that what we do in solo and group practice (history, physical examination, laboratory testing, x-ray, diagnosis treatment) is the only level of relationship expected of us? Can we do more and should we in medicine, assume the obligation of other bankrupt social institutions? And if we should fail, would we be blamed for not delivering on a social contract, if bankrolled by public funds?

Now is the time for medicine to engage these problems squarely, and subject our care activities to rigorous comparison. I believe this is the least we can do for the new physicians who have now elected primary care, but shortly because of a lid on subspecialty training, will increasingly be shifted subtly into primary care fields. Will the individual personality, skill and desires of the resident fit into the primary care mode of practice? Will the new graduates endorse the "new" specialty and the new epidemiology? Or will they behave like a conscript into indentured service? It would seem from the anecdotal observation of The Robert Wood Johnson Foundation program directors that the present applicants come from the top quarter of their class, and are indistinguishable on the wards from their more traditional colleagues. Healthy skepticism should recognize that significant departure from the traditional will always attract the intellectually adventurous. More than that is needed to hold them. If the new specialty does not have the substance to attract new graduates, disillusionment will soon set in and snowball forward and backward—erupting anger in those who have been sold a "bill of goods," and creating revolt in the ranks of those who will select (or be selected) for primary care.

Now is the time to begin developing the intellectual abstracts in the field of primary care.

1. What are the benchmarks of primary care? Is it more than a collection and parade of superficial specialties? Do family practitioners make a

difference in treating patients in a family? Is the individual better and the family constellation better for it?

2. What are the research programs under way? Are there enough "career development awards" for young faculty to wrestle with the substance of the field—and once accumulated, can the data be accumulated and transferred with reasonable certainty from generation-to-generation?
3. Is primary care medical practice—in neighborhood health centers, group practice, HMOs—doing anything about the new morbidity and new epidemiology? Are the complaints for which people come to physicians—complaints about which we can do anything about? What evidence is there that primary care prevents, anticipates or corrects incipient illness?
4. Are the practice models we now know too conventional—is conventional wisdom about practice locked in? It is frightening to visualize that Washington health planners are rapidly preparing guidelines, regulations and data about medical practice which may lock us into procedures and testing that the public will expect and we will have to deliver—with the full realization that they do little good and maybe some harm.
5. What evidence is there that the present practice models are appropriate and suitable for the new epidemiology? Are the frenzied activities in EST, biofeedback, yoga, and relaxation response consumer rip-offs, or are they genuine aspirations (still not definable in scientific or medical terms) that can be incorporated into the medical model?
6. If primary care expands with more doctors doing more things, and secondary and tertiary care continue their activities, where is all the money to come from? Will we be a society in which we spend a good deal of our working hours and GNP with health? Can substantial portions of primary care be delegated to families, individuals? Do Americans retain some of the self-reliant qualities as expressed by isolated missionaries, Peace Corps volunteers, the military—or are they so swamped with other acute demands that they prefer to transfer their medical and social and quasi-medical problems to the physician? Have we experimented enough with self-care to equilibrate the pressures that will rise (both in demand and cost) for ever-increasing care?
7. Are "teams," which include internists, pediatricians, and physician extenders a model that is reasonably cost-effective and comfortable for patients, or could it fragment under the pressure of separate reimbursement, so that patients will have to negotiate with another level of fragmentation of care?
8. What of geriatrics? Is this a new specialty on the horizon since proven neurochemical and biological differences exist (e.g., pediatrics), and can the need for physicians who deal with this emerging problem be dealt with in family medicine and internal medicine faculty development (Table III)?

Although there may be other training sites equally or better situated, I would suggest that philanthropic and federal funds be carefully allocated to

TABLE III

The Elderly in the Population[3] *and Hospital Days*
Projection comparison between 1971 and 2001

Year	Number over 65	% over 65	Hospital Days
1971	1.7 million	8.1	35%
2001	3.3 million	10.9	42.5%

stable service and training programs so that these questions and hypotheses might lead to data that is accurate, and conclusions about the investment in primary care that will gather public support. The nation is experiencing a retraction of its former economic expansion, and whether all things are affordable is open to question. Experience in other countries indicates that "home-based and community-based care remains the distinctive feature in Britain. It is such kindness-centered features that now are most threatened, for dwindling national wealth can no longer support the community health and social support services upon which this fragile balance of integrated care depends. If social stability in the United Kingdom declined to anything like the extent of that in urban America, it is doubtful if the primary-health-care component of the National Health Service could survive in its present paternalistic form. History suggests that social stability and attitudes and the desire or necessity for radical change usually originate in economics. In an economically shrinking world it is reasonable to assume that physicians and their patients will experience and will adapt to profound changes in the conditions under which medicine will be practiced at the primary level (5).

At present, The Robert Wood Johnson Foundation programs are undergoing an extremely extensive review by the University of California at San Francisco. Early data from these programs would seem to indicate or reconfirm that:

1. The decision to enter a primary care residency is made either before entry to, or during, medical school. Our data indicate that of the residents studied, 80% made their decision prior to leaving medical school. These data, I believe, are quite consistent with data obtained by Dr. Daniel Funkenstein at the Harvard Medical School.

2. A corollary of this "fact" is that of the residents who attended medical schools where a primary care curriculum track or primary care elective were available, almost 85% opted to "track" or take the electives. Undoubtedly medical schools can influence career decision, and your [the author's] comment about *substance* is equally applicable to medical schools.

3. As with other residency programs, primary care programs have problems related to financing and space. Our data indicate that about half the programs cite funds and space as continuing problems.

4. Many programs indicate that the lack of qualified teaching faculty is a continuing problem. Only in programs affiliated with the nationally accepted prestigious medical schools is recruitment of qualified faculty not a problem. We have found that four out of nine programs describe this as one of the many problems they have encountered and continue to struggle with. Since the quality of a faculty is a direct influence on the substance of a program, it is important to stress the need for programs to develop qualified faculty to assume teaching positions in primary care residencies.

5. Our demographic data indicate that minorities are not being attracted to primary care residencies in any great numbers. Asians, Blacks, and Latinos continue to avoid primary care. The same can be said for females, except for one or two notably exceptional programs (6).

Summary

Over the past five years an important and documented shift has taken place at an increasing number of U.S. medical schools and training hospitals as opportunities develop to educate and train physicians in primary care. Concurrently, additional, or more likely substitute, dollars shifting from other competing programs, will be made available to these primary care residencies which will force our academic institutions to rethink their graduate training and service requirements.

On-line evaluation and monitoring will be crucial to accumulate data as to the appropriate selection, setting and faculties for these efforts. Is it cost-beneficial and less confusing for patients to have multiple access into primary care, or should attempts at consolidation between family practice and internal medicine/pediatrics take place to produce a "unisex" primary care physician? Additionally, closer and more functional relationships should develop between trainers, practitioners, financing mechanisms and patients to broadly outline what is expected and what is possible under future financing schemes.

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The Medical Specialist as a Primary Care Provider

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Introduction

Primary care has become the catchword of American medicine. Both in town and gown, primary care is the "in thing"; academic medical centers are training more primary care physicians as family practitioners, internists, pediatricians, and, in some instances, obstetricians. There is hope that the decline in the number of general practitioners—newly rechristened family physicians—and general internists entering practice that had been evident since 1950 is being reversed.

What are the reasons for the upsurge in primary care training and practice? Firstly, there is the perception that medical care rendered to a patient by several physicians is too fragmented and centers attention on "disease" rather than "patient." The consequence of this system has been characterized as "too scientific" and not sufficiently "humane." Perhaps equally important is the notion that care rendered by multiple-specialty-oriented physicians is more expensive than that provided by a single physician. Whatever the reason, there is a current ambience that the public is entitled to more primary care physicians and this has been mandated by law (PL84-484). Public Law 84-484 mandates that by 1980 fifty percent of trainees in graduate programs must be engaged in preparing for careers in primary care defined as family practice, general internal medicine, and general pediatrics.

The Contract for Primary Care

At a seminar held in October 1974 (1), the rhetoric dealt with the competition between family practice on the one hand and internal medicine and pediatrics on the other for the "contract for primary care." This rhetoric has, fortunately, to a large extent subsided. The pluralistic character of our health care system makes it unlikely that any one specialty will be privy to providing the majority of primary care in this country. The very nature of training patterns also militates against this. In 1976, for example, approximately thirty percent of the first year graduate trainees in this country were in internal medicine, ten percent in family practice, and ten percent in pediatrics. Others, some of whom will also engage in primary care, were in "flexible" training programs. Of the large pool in internal medicine, too many are presently continuing their training in the subspecialties; the majority of the trainees in internal medicine

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now in the pipeline must opt for general internal medicine—or primary care—as a career. In addition to the traditionally defined primary care specialties, a number of subspecialists in internal medicine and even surgery provide primary care. Not the least well defined among the groups claiming a piece of the primary care pie are the physician extenders whose role in the health care system remains poorly defined. Without extending these arguments any further, it is safe to say that no group of physicians possesses a territorial imperative; indeed, it is essential that each group interested in providing primary care place the struggle for the territorial imperative behind it and address the problems that affect the primary care movement.

Definition of Primary Care

Most definitions of the primary care physician describe a provider who (a) serves as the first contact for the patient in the medical center, (b) is able to care for most of the patient's health problems, (c) follows the patient over a long period of time, and (d) coordinates for the patient (and sometimes for his family) the use of other providers of medical care. In some definitions of primary care, care of the total family is emphasized. However, there is an important difference between family practice, on the one hand, and internal medicine, pediatrics, and obstetrics on the other. In one model the entire family receives care from a single physician, and in another internists, pediatricians, and obstetricians combine to provide primary care for each individual family member. We do not wish to claim superiority of one model over the other; we simply wish to point out the difference. No matter what the parent discipline, however, there are certain attributes essential to the practice of good primary care. These are accessibility, comprehensiveness, coordination, continuity, and accountability (2).

Accessibility means that services should be conveniently located, available twenty-four hours a day and acceptable to patients on a financial and psychosocial basis.

Comprehensiveness refers to the willingness and ability of the primary care physician to handle the majority of the problems arising in his patients. Implicit in this definition of comprehensiveness is the right of the primary care physician to choose the population of patients he will serve.

Coordination entails the appropriate use of consultants and integration of the information that derives from consultants into the health care plan of the patient. It also suggests that the individual's health care plan must be compatible with his financial, family and occupational circumstances.

Continuity includes follow-up care including pursuit of noncompliant patients. Accurate, accessible patient records are increasingly important in achieving continuity of care.

Accountability includes willingness of the physician to submit his practice to various quality assurance activities including studies of process and outcome, participation in educational programs to upgrade the quality of practice, maintaining appropriate informed consent, engaging in patient education, and taking responsible measures to control the cost of health care.

The primary care internist differs from his counterpart in family practice because, for the most part, he confines his practice to the care of adults. He is concerned with most diseases of adults and has become adept at handling disease processes in multiple organ systems. The result of his more extensive training in internal medicine is his greater depth of knowledge of disease; this is without question greater than that of his counterpart in family medicine. A trade-off is, of course, that he is much less knowledgeable in handling problems of children, pregnant women or manipulative procedures. The primary care internist usually also maintains considerable adeptness at caring for acutely ill patients in the hospital. It has been argued that internal medicine is an inefficient vehicle for the provision of primary care because internal medicine does not involve a high volume of patients. However, as noted recently by Kane (3), the practice of primary care may contraindicate a high volume of patients because a good primary care physician must spend a good deal of time with his patients. The three C's of primary care—comprehensiveness, continuity, and coordination—take time, not to mention the three C's of the patient—convenience, compassion, and competence (3).

Training of Primary Care Internists

During the last two decades, training in internal medicine has, by and large, emphasized subspecialties of internal medicine as they pertain to inpatients. Any training programs that substitute categorical specialty units for general medical wards, and even those that maintain general medical services, emphasize consultations with the subspecialties. The focus has been on acute care and intensive care. Relatively little training is provided in the outpatient setting. The relentless drive to training in the subspecialties has been to a large extent fired by bursts of the technical advances that have characterized the practice of many of the subspecialties in internal medicine.

In an attempt to improve the preparation of internists training for the practice of general medicine, a number of departments of medicine have developed training programs in internal medicine, the so-called primary care tracks. The major differences between these tracks and the traditional training programs are:

(1) Increased emphasis on training in an ambulatory setting. In some programs as much as fifty percent of the resident's time is spent in the outpatient department, as opposed to less than ten percent in most traditional programs.

(2) Patient-care continuity is an important part of the training experience. Although some of the traditional programs offer a continuity experience by permitting house officers to care for patients on a weekly basis, exposure to outpatient medicine in the primary care tracks is much more intense and may encompass as much as half of the resident's time.

(3) Introduction into training programs of disciplines that traditionally have not fallen under the aegis of internal medicine. This includes office gynecology, nonsurgical musculoskeletal problems, nonsurgical otolaryngology, ophthalmology, and dermatology.

(4) Increasing emphasis has been given to behavioral medicine, psychosomatic medicine, and psychiatry.

(5) Introduction of medicolegal and business concepts into the resident's training.

The goals of the primary care training programs in internal medicine are summarized by Young (4):

> The developing internist not only should begin to acquire knowledge and skills in dealing with ambulant patients but he also should develop attitudes, interests and value systems that will place ambulant patient care in perspective with secondary and tertiary care in the hospital . . .
>
> An internist must learn, particularly in this setting, to be satisfied with small gains which mean much to the patient in terms of satisfaction with daily living but may not at first seem as rewarding as the dramatic response of a patient with pneumonia, heart failure or pernicious anemia. An internist must learn to be interested in patients as people and not merely in their diseases. Our mission is to help patients live healthier, happier lives. Making exceptionally astute diagnoses and effecting dramatic cures are only small parts of the physician's work in the real world of health care.

Primary care training in internal medicine has required the recruitment of new faculty. Such recruitment has taken place at some institutions. In contrast to classically trained faculty that populate departments of medicine and usually have a specific interest in a subspecialty, the primary care faculty have particular interest in patient care and methods of health care delivery. Individuals must find the right formula to serve as role models for general internists in the way that section heads of subspecialties serve as models for future subspecialists.

Obstacles to Achieving the Goals for Primary Care Training and Practice.

Despite the announced government position where fifty percent of graduates of American medical schools must enter the primary care specialties, there are some serious problems which confront primary care. Some of these are detailed below:

(a) Adequate funding for residency training positions. In excess of 15,000 individuals are being graduated from American medical schools each year and it is the conventional wisdom that nearly 8,000 of these must go into primary care. There are not at the present time enough first year residency positions in the three primary care specialties to accommodate the need. If positions of borderline quality which have not attracted the American graduates for many years are eliminated, there appears to be a need for approximately a thousand additional first year primary care positions. Moreover, this assumes that all individuals that enter primary care residencies will practice a primary care specialty and this is, of course, not the case. Internal medicine and pediatrics, at least, have a significant number of trainees who enter a subspecialty following completion of three years of residency in internal medicine and pediatrics. There are also a few defections to academic medicine from internal medicine, pediatrics, and family medicine. These losses must be accepted if the next generation of academicians and investigators is to be trained, and it may be logical to add even more primary care training positions than the thousand that are needed. At the present time, then, there is not adequate support for training spots for general internal medicine. The situation is somewhat better for family medicine which has received a good deal of support for residency training from state legislatures but has a dearth of teachers and programs in teaching hospitals. A training position has little meaning unless it is supported financially. For the most part residency positions are paid for by patients admitted to hospitals. Training in primary care involves extensive time in the community setting, and most hospitals have no way of supporting this training. There is, then, an urgent need for public subsidy of primary care graduate training positions, particularly in internal medicine.

(b) Obtaining facilities for primary care. The decrepit clinics that are the hallmark of general teaching hospitals which depend on indigent patients are not an appropriate vehicle for training in primary care. To an extent family medicine centers have overcome this obstacle by providing attractive facilities at the cost of considerable financial stress on their parent hospitals. Even if these centers are manned by family physicians who have brought their own patients from their former practices, they have required considerable subsidization from grants or the parent medical school. Internal medicine has enjoyed no such subsidy; the general medical clinics are the disadvantaged of primary care. Moreover, in contrast to family medicine centers, internal medicine clinics must pay for themselves by charging professional fees by the faculty teaching in these clinics. When this fee is added to the charge made by the hospital for the use of the facilities, the combined total often exceeds that charged by internists practicing in the community. This provides a distinct disincentive to patients who wish to receive comprehensive care in university-based medicine clinics. There is some doubt in our minds that primary care facilities can ever exist economically in tertiary care teaching hospitals. Teaching hospitals characteristically have high overheads (that are passed on to their operating units including internal medicine clinics) and ineffective personnel policies, both of which have conspired against making these clinics effective settings for primary care practice. Such mundane matters as parking, which can be costly and inconvenient, also interfere with patient access to the clinics. These problems have led us to the conclusion that the best place for a primary care facility is not on a university campus or in a tertiary care hospital. Instead, these clinics should be developing facilities off campus so that efficient primary care can be provided. Such off-campus primary care facilities would encompass family practice, internal medicine, pediatrics, routine prenatal and postpartum care, and some aspects of psychiatry. It would include preventive services, sex counseling, and would employ a significant number of health care extenders. The advantages of this proposal are considerable. Care rendered in such a setting should be more economical, more pleasant, and more accessible. It would provide sound and more realistic teaching and should result in better patient acceptance. It would be less in need of subsidy and would provide an environment that is closer to that of the "real world" of practice.

(c) Readjustment of fees. The practice of the primary care physician is based on ambulatory and nonprocedure-oriented medicine which has a fee schedule far below that of physicians who perform procedures, regardless of how simple the procedure is. More equitable fees are needed for ambulatory care so that primary care physicians can make a reasonable living without resorting to the use of scalpels, electrocautery or other technologic devices, or the operation of laboratories which also tend to be lucrative. Although economic incentives are not the primary determinants that push individuals into medicine or that determine their choice of specialty or location to practice, they certainly contribute to these decisions.

(d) The place of the general internist in the academic setting. Generalists have difficulty in finding their place in the academic setting in an era of specialization. Because of the sharp increase in knowledge in all spheres of biology and medicine, specialization is progressing despite the hue and cry that it might not be in the best interest of the patient. For example, we find that hematologists have subdivided the field, and there are now red cell specialists, clotters, and white cell doctors; in the surgical subspecialty of otolaryngology there are otologists, throat doctors, and plastic surgeons. By focusing on a comparatively narrow area, a physician can amass a great deal of knowledge and, if he is in the academic setting, his clinical expertise and research productivity will enable him to be recognized as an expert even though his area of expertise may be relatively small. This can hardly ever be the case for the broader generalist who has difficulty in meeting the requirements of the reward system. The generalist differs from the subspecialty faculty member in several ways: (1) Because of his breadth and interest in health care, he is spread very thin. All too often he is on every committee and task force dealing with quality assurance and other aspects of the health care bureaucracy such as PSRO, HSA, etc. (2) He is heavily committed to the care of patients which often places enormous demands on his time. (3) He is likely to be in demand as a teacher. Not infrequently his teaching will take place in the community away from his home base, entailing considerable inconvenience because of the time involved. (4) He usually does little or no research, placing him at a major disadvantage when promotion time rolls around. There are several reasons for this lack of research productivity. Firstly, the clinical, teaching and administrative functions of the generalist often do not leave him much time for research. Secondly, research in health care or epidemiology, the areas in which these faculty should work, is difficult; results come slowly and often do not enjoy the credibility accorded by publication in prestigious journals. Finally, the generalist's role in teaching is often less dramatic and less appreciated simply because it occurs in a one-to-one situation in the ambulatory setting.

The outpatient department is not the place for dazzling diagnoses or stunning therapeutic triumphs. In a way, the generalist is the affirmative action product of our academic medical centers. We appreciate the need for having these individuals on our facilities and go to great lengths to recruit them. Once they are recruited, however, they are deluged with clinical, teaching and administrative commitments which make it difficult for them to progress along the usual academic channels. We must find a way to reward the generalist. He rarely gets to go to international congresses and he does not see his name in print very often, but we must find a way to accord him recognition. Promotions and tenure committees must learn to recognize that this faculty's excellence lies in teaching and patient care and that they serve as effective examples for general internists of the future. In our view, the creation of different types of academic ranks is not the way to solve the problem. The more traditional promotion process has promulgated high standards of excellence and it is necessary for the faculty on promotions committees to recognize that the standards of excellence for generalists are different but no less rigorous than those established for clinical investigators.

Is There a Role for General Medicine in the Health Care System of the Future?

On a more philosophical note, we would raise the question whether the resurgence of primary care in general, or general internal medicine in particular, is not flying in the face of history. The rapid expansion of the knowledge base raises the specter of the generalist who knows less and less about more and more. Is not specialization the answer to the progressive increase in knowledge? Does not the attempt to train more general internists fly in the face of manpower predictions? As more specialists are trained will they not migrate to the small communities and provide a more sophisticated type of health care in that setting? Also, does the primary care movement not fly in the face of public expectation? Certainly, the public wants readier access to health care and they pay lip-service to humanism, empathy and house calls, but when they really get ill do they not want the most skilled and scientifically advanced care available? We never cease to be amazed by the health care planners and other spouters of antimedicine rhetoric who espouse health care extenders but who want the best subspecialist when they or a member of their family become ill. The answer to these difficult questions is not at hand, but if they turn out to be: (1) that the knowledge base is expanding too rapidly for any physician to be broad enough to master a significant amount of it and; (2) that the training patterns in this country have predetermined that the road to specialization for the majority of our physicians is inevitable; and (3) that the public really equates specialty medicine with the best medicine, then the primary care movement will atrophy and both the family physician and the general internist will disappear.

We hope intuitively that the answers to these questions will be negative. We believe that generalists can be excellent providers of health care both among the well and the sick. This means that the general internist must maintain himself as a physician of the highest quality, up-to-date, intellectually curious and highly skilled. This also means that the general internist must receive the best training that is available. Moreover, it is incumbent upon such an individual to embark on a course of lifelong learning and it is equally essential for the academic establishment to provide him with learning opportunities throughout his professional career.

Conclusions

We accept the premise that generalists are needed. These general physicians must come from at least three parent disciplines—family medicine, internal medicine, and pediatrics—and probably from many more. In internal medicine there is a need to restructure the training programs to place greater emphasis on ambulatory care, on some noninternal medicine specialties while maintaining areas of excellence which have been the hallmarks of internal medicine training programs. There is also a need for a new type of faculty member to head internal medicine training. In order to recruit such faculty members, the reward system should be adapted to give more credit to excellence in teaching, clinical care and broad-based epidemiologic and health care research. Other problems must be overcome in the training and practice of general internal medicine to achieve the renaissance that is necessary. This includes creation of new training positions in internal medicine, construction of more efficient and effective facilities for the provision of primary care, a realignment of fees to reward ambulatory nonprocedure-oriented medicine rather than procedure-oriented manipulative medicine, and, finally, to provide academic recognition for general internal medicine faculty.

We have discussed whether primary care is really the ideal mode for the American health care system of the 1980s. We intuitively feel that it is, but only time will tell.

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Primary Care at a Teaching Hospital: History, Problems, and Prospects*

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Beth Israel Hospital in Boston, Massachusetts is a 432-bed university-affiliated teaching hospital that serves as one of the major educational facilities of the Harvard Medical School. In October 1972, the clinics in General Medicine, Pediatrics, and Obstetrics/Gynecology were replaced by a primary care program called the Beth Israel Ambulatory Care Center (BIAC) (1). This report intends to give a frank portrayal and analysis of the development of BIAC, with particular attention to the organizational consequences of basing such a program in a teaching hospital. Many of the issues we discuss remain unresolved. We write with the hope of stimulating similar efforts and workable solutions to some extremely complex problems.

The discussion is divided into three parts: 1) a contrasting description of the status of primary care at the Hospital before and after the development of BIAC; 2) an analysis of some of the forces and events that led to the evolution of the BIAC concept, with emphasis on organizational development; and 3) an evaluation of problems and prospects that the program faces in its sixth year of operation.

I. Primary Care at Beth Israel Hospital before BIAC

In 1971, when the initial thoughts about BIAC were evolving, the general clinics were intended to serve the primary care function of the Hospital. They were organized similarly to those in other teaching hospitals, with house officers and part-time voluntary staff physicians providing the care. In the medical and pediatric units, staff managed patients on an appointment basis, working without pay one-half day per week. Their obligations did not extend beyond this session, and there was no provision for continuity of care. Moreover, clinic patients were asked to avoid visits to staff physicians in their private offices, and indeed they were actively discouraged from trying to transfer their care to such physicians. House staff, who also attended clinic once a week, took varying degrees of continuing responsibility for their patients, depending on individual levels of commitment. At times, house officers managed their clinic patients during hospitalization and through subspecialty referral routes, but this was the exception. The obstetrics/gynecology clinic, in contrast to the medical and pediatric clinics, operated through block sessions,

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with patients managed on a first-come, first-served basis. It was unusual for a patient to see the same provider on subsequent visits.

While in the clinics, house officers were essentially on their own. Teaching was sporadic, with little organized activity, and in some of the units there was no attempt to teach at all. When consultation was required, it was carried out on an ad hoc basis, with senior house staff or attending physicians called to provide consultation in their given sphere of interest or expertise. Patients requiring hospitalization were admitted to the "chief's service" where they were managed by house officers supervised by the attending physician of the month. In the Department of Medicine, house officers who managed such patients during hospitalization frequently took responsibility for their continuing care thereafter, but in the obstetrics/gynecology and pediatric units there was no practice directed toward continuity of care.

Patients were able to seek out specialty programs such as the cardiology or infertility clinic at their own initiative, and there was little organized attempt to define boundaries between primary care and subspecialty needs. When chiefs of the medical subspecialty clinics were polled, the general response was that 50% of the patients seen in a given unit were there by default, with problems not truly appropriate for subspecialty services.

Patients came to the outpatient clinics by habit, frequently with the perception that they had no access to private care, in part because they would be unable to pay private fees. No patients were turned away from the clinics because of inability to pay. Flat fees were charged for clinic visits without regard to the type of service or the length of visit. In 1971, the average fee was $16.00 per visit, and this was said to represent the cost per visit to the Hospital. There is little data available documenting the actual revenue generated from such billings.

The chief advocates for the patients were house officers, several social workers and staff nurses who worked in the area, and administrative personnel responsible for the system. There was little formal process for handling patient complaints.

The clinics stood in sharp contrast to the private practice of the part-time staff whose offices were generally close to the Hospital. They were also very different from the small suite of private offices three floors above the clinic where private patients were seen by the full-time Hospital faculty.

II. BIAC Today

A. *Delivery System*

Today BIAC manages approximately 15,000 patients, with 43,500 visits annually on a fee-for-service basis (Table I). Patients are drawn from a varied ethnic, socioeconomic, and residence base, with the practice serving a richly varied population (Tables II and III). BIAC has replaced the above-mentioned units with a group practice of faculty physicians, nurse-practitioners and midwives, social workers and psychiatrists, working in teams which provide care in a way which we feel is quite consonant with the requirements for quality primary care that have recently been promulgated (2, 3).

TABLE I

Primary Care Patient Visit Volume

Fiscal year		Patient visits
Before BIAC*		
	1969–70	23,208
	1970–71	24,980
	1971–72	29,144
BIAC		
	1972–73	33,020
	1973–74	41,650
	1974–75	46,743
	1975–76	47,129
	1976–77	43,529**
	1977–78 (projected)	43,500

* Represents visits to the general medical, obstetrics/gynecology and pediatric clinics, which have been eliminated and replaced by BIAC.

** BIAC pediatric unit closed March, 1977.

TABLE II

BIAC Patient Population—FY 1976–77
*(Includes Medical, Ob-Gyn and Walk-In Units)**

	Percent
A. Primary Payment Source (by patients, *not* visits)	
Self pay (full and partial pay)	35
Medicaid	20
Blue Cross	18
Other Private Insurance	9
Medicare (Medex)	10
Compensation and Grants	1
Employees	7

	Percent
B. Age Distribution (by patients, *not* visits)	
75+	3
65–74	7
55–64	8
45–54	6
35–44	7
25–34	29
13–24	34
12 and below**	6

* Mental health visits are integrated with each unit.

** Pediatric Unit closed March, 1977.

The practice is covered 24 hours a day, seven days a week. When patients require hospitalization or referral to subspecialty units, they are managed as private patients of their personal BIAC physician. Part-time voluntary physicians no longer practice in the unit. A walk-in unit is managed primarily by a nurse-practitioner who works as colleague and teacher to senior medical residents who rotate through the unit. Thirty percent of all visits to the BIAC program are to nonphysicians—to "new health practitioners" who function as full partners on the individual teams. Mental health care is integrated fully into the delivery system, with the BIAC psychiatric and social service staff functioning both as consultants to other team members and as direct providers (4). There is an active home care program closely affiliated with BIAC; patients who require nursing home or recuperative facility follow-up remain under the care of their BIAC physician.

In March, 1977, the pediatric component of the BIAC practice was merged with the Comprehensive Child Health Program at the Children's Hospital located 100 yards from Beth Israel Hospital. The practice is coordinated with BIAC, affording opportunity to integrate management of families in the two programs.

The obstetrics/gynecology program is increasingly active. In 1972, 22% of Beth Israel Hospital deliveries came from the BIAC program, but at the time of writing, 35% are derived from the BIAC practice, with an annual total of 700 deliveries in BIAC representing a 40% increase in deliveries since the start of the program. Nurse-midwives play a major role in the unit. With the recent passage of legislation entitling them to conduct deliveries, we have developed an "alternate birth center" in which patients may choose to conduct both labor and delivery, attended by the midwives who cover the practice 24 hours a day, seven days a week in parallel to the BIAC obstetrician/gynecologist.

B. *BIAC Education Programs*

The education program in BIAC is varied and active. Students of medicine, social work, nutrition, a psychiatric fellow, and nurses in practitioner educational programs work as apprentices to the nuclear faculty team of physician, nurse midwife or practitioner, social worker and nutritionist. They join the practice to the extent that their training permits, participating in the multiple teaching conferences that are held each week. In addition, all house staff in medicine and obstetrics/gynecology practice in BIAC, managing patients during their Hospital training while supervised by the faculty teams. House officers provide continuity of care to their patients, and the faculty teams serve an umbrella function in backing up those house officers who are unable to manage their patients when other responsibilities intervene.

TABLE III

BIAC Medical Unit Patient Population

(excludes Walk-In Unit)

	Percent
*Age Distribution**	
(by patients, *not* visits)	
15–29	33
30–49	32
50–64	17
65+	18

* Patients making one or more visit to BIAC Medical Unit over two year period, 1975–77.

In addition, as part of a Harvard-wide program, there is a special track in the Hospital Department of Medicine for house officers who wish to have an intensive experience in primary care and general medicine education. After the traditional internship (PG I) year, those who enter the primary care residency spend six months of each of the two subsequent years (PG II and III) in ambulatory care. This part of their education is in turn divided into two parts: a) they join the BIAC practice and manage a panel of approximately 150–200 patients in concert with a faculty team; and b) they rotate through the various medical and nonmedical subspecialties which are particularly relevant to primary care education (5). In addition, they participate in a program linking general medicine practices in rural settings to the BIAC unit. During one or two rotations of about six weeks in length, they gain a sense of primary care practice in settings far removed from the academic health center. Twenty-five percent of house officers in the Department of Medicine training program are in the primary care track, and in recent years there have been more applicants from the intern pool than can be accepted for the program. Detailed description of similar programs can be found elsewhere; it is beyond the scope of this discussion to describe our own at length (6).

C. *BIAC Research Activities*

Activities in both clinical and health services research are steadily increasing in BIAC. In an attempt to inquire further into the nature of patient-provider communication, we are conducting an experiment to assess the impact of having patients and providers jointly author the medical record, with the patient maintaining a copy in his or her own possession. Research into the economic impact of the primary care education program has compared ours to similar programs in different practice settings (7). We are attempting to sort out different categories of psychosocial problems our patients face, with the hope of focusing more crisply on realistic therapeutic approaches in the medical setting (8). The research is increasingly interdisciplinary in nature, and links have been established between BIAC and the Center for the Analysis of Health Practices at the Harvard School of Public Health.

The BIAC practice forms also a focal point for clinical investigation directed toward the ambulatory patient. Studies have included the use of patient management protocols for acute and chronic illness (9, 10). Projects are underway in clinical pharmacology, evaluating the causes of disability in the elderly, pathogenesis of common mild infections seen in ambulatory settings, etc.

The program has now completed its fifth year of operation, and with this necessarily brief contrasting description, we can step back and trace some of the origins of BIAC.

III. Stages in Development

In the early 1950s at Beth Israel Hospital, Solon, Sheps and Lee, in a series of now important historical papers, analyzed the outpatient population and pointed out that not all seeking care were coming to the Hospital for the same reasons (11). The patients' perceived needs ranged from viewing the Hospital as their principal primary provider, to receiving episodic care for intercurrent illness, or to seeking subspecialty consultation. These observations led to improved services for the clinic patients (12), but financial impediments and the "second-class" nature of outpatient services precluded large-scale organizational change at that time (13).

Probably the most important ground work for the development of BIAC came in the mid-1960s. In order to develop a one-class system of care for all inpatients, the decision was made to eliminate the wards which had been reserved for the medically indigent. All patients were declared thereafter to be "teaching patients"; medical students, house officers, and fellows were to have access to all patients, whether referred and managed by private part-time physicians, or coming from the outpatient clinics or emergency unit. This program was successful and served also to attract increasingly talented house officers to the Department of Medicine and the Hospital as a whole.

Planning for BIAC began shortly thereafter. Three principal objectives were articulated: a) to develop a one-class primary care delivery system serving at reasonable cost all those who chose to view Beth Israel Hospital as their provider; b) to graft onto such a system an educational program which it was hoped would attract young health care providers into the area of primary care; and c) to encourage both clinical and health services research which would make BIAC worthy of its role in an academic health center. As the program was developed, two other objectives played additional central themes: a) to establish an appropriate degree of autonomy for the program so that it might best operate in a setting which perforce centered much energy on inpatient activities, and b) to develop an interdisciplinary team practice which integrated mental health and medical care in one unit.

Initial thinking of the planning group of trustees, clinicians, and administrative personnel led to the concept of the Beth Israel Ambulatory Corporation. We emphasize the word *corporation* because one of the first realizations was that, for such a project to succeed, it should be to a great degree administratively and fiscally separated from the parent institution.

The planning group decided that an explicitly negotiated cost-revenue center would have to be created to identify the direct and indirect costs of outpatient care and the revenue generated therefrom. It determined that only with complete financial itemization and documentation could BIAC avoid the time-honored problems posed by assigning to the outpatient budget "costs" that had little to do with the actual services rendered (14). This insight was bolstered by the fact that the $16.00 average clinic fee in 1971 was said to represent "cost" for a visit and existed in a unit without salaried physicians and with inadequate support staff. Yet at the same time it was higher than the prevailing fee set by the private practitioners in the community. Analysis of the cost figures indicated that personnel from departments which were at best indirectly engaged in ambulatory care activities were charged off to this unit. It was clear that before the prospect of bringing on full-time salaried faculty physicians etc. could be entertained seriously, appropriate costs and revenues would have to be isolated. It was decided further from the start that every attempt should be made to segregate the costs of the educational and research activities from those of the delivery system as such.

With the opportunity for six months of relatively sheltered time for planning and development, a proposal was executed and presented to the Hospital Trustees. Funding agencies were asked to support that percentage of faculty and administrative time devoted to developmental activities, teaching and research. We were fortunate in attracting the promise of relatively large sums of money from private foundations.

We spell out these details because these developmental seed monies were exceedingly important in helping convince the Hospital Trustees and clinical chiefs to go ahead with such a program, even though many aspects of it were viewed as potentially threatening not only to aspects of the Hospital teaching programs, but also to the private staff physicians. While it was difficult to argue with the concept of improved ambulatory services offering a one-class sytem of care similar to that which was under way on the inpatient side, some difficult questions were posed. What would happen to "teaching" patients, particularly in the surgical specialty of obstetrics/gynecology, if full-time physicians were recruited to care for many of those patients who had theretofore "belonged" to the house staff? Could continuity of care be offered to such patients while teaching house officers to assume increasing degrees of patient care responsibility? How would Hospital sponsorship of full-time, Hospital-based practicing physicians be viewed by the private staff? Would this lead to conflict detrimental to the perceived needs of the Hospital? If a true cost-revenue center were developed, and the Hospital and third parties were forced to reallocate costs heretofore allocated to the outpatient department, what would be the net fiscal impact?

Perhaps the most difficult questions were posed by the Trustees: what would happen when the initial grant support and excitement generated by new leadership disappeared after the early stages of the program? Could the delivery system support itself? Would national health insurance exist to help each patient pay the bill? How much would the education program cost, and how should it be financed? Would there be continued research monies available? In sum, might the program prove to be still another model that rose and fell according to the fortunes of soft money and transitory leadership (15)?

These are the questions that were articulated most clearly. We expected several others which were not raised, but which have been posed frequently in similar ventures at other institutions. If there were competition for Hospital beds, who would get the bed, the hospital-based group practice or the referring private physician? At our Hospital this was not a pressing problem because an expansion of beds was imminent in 1971. A more subtle question related to the impact of such a system on the net bed utilization. Would the practice grow such that there was a net increase in beds occupied, or would the character of a primary care practice be such that those who had been hospitalized in the past might now be managed on an ambulatory basis, with a net egress of inhospital patients in a hospital whose balance sheet depended in good part on bed occupancy?

We shall return to these and other issues, but first will describe the organizational approach to the program.

A. *Organization*

The initial organization of BIAC was developed at three levels. The first, a supervisory, planning group, was to focus the Hospital administration, clinical leaders and trustees on the program. The group consisted of the Physician-in-Chief, Obstetrician/Gynecologist-in-Chief, General Director, Director of Fiscal Services, a trustee, and two health professionals who had particular expertise in primary care. The role was to approve, direct, and modify the program as it was articulated jointly by the Medical Director of Ambulatory Care and the Assistant Director of the Hospital for Ambulatory Services. The group met approximately every six weeks, but ceased meeting in 1974 and thereafter.

BIAC leadership formed a second level. The "core staff" consisted initially of the BIAC Medical Director, Assistant Director of the Hospital for Ambulatory Services, BIAC Social Services Coordinator, BIAC Psychiatrist, Assistant Director of Nursing for Ambulatory Care, and the Assistant Administrator for Operational Activities. Recently, the BIAC Chief Obstetrician/ Gynecologist joined the group. Meeting weekly, this group is designed to function as both the BIAC planning and monitoring unit.

The third level was established at the line. The responsibility for patient care is held by faculty teams whose nucleus consists of a nurse practitioner or midwife, physician, social worker, and nutritionist, assisted by a secretary/receptionist and health aide.

We turn now to an analysis of these three groups, examining the elements we feel have worked well and also not so well. The central theme for the discussion that follows may be taken as: what would we do differently if the opportunity came again, and what has yet to be done? We offer this, aware of the hazards of trying to generalize from our experience, but with the hope of helping others avoid reinventing a wheel which, at times, has been thoroughly tested in our program.

The supervisory group of Hospital leaders quickly ran out of steam. We learned that the most pressing issues were best resolved on an ad hoc, small group basis. From the point of view of BIAC leaders, meetings served little more than a carefully orchestrated "show and tell" function; from the point of view of Hospital leaders, BIAC's problems frequently paled in comparison with some of the inpatient priorities. On occasion the meetings proved useful (from the BIAC vantage point at least) in "educating" the Hospital leaders about issues a primary care program faced, and at times group pressure came to bear on one of the clinical chiefs, the Director of Fiscal Services, etc., with outcomes which, at least in the eyes of the BIAC leadership, proved helpful.

On the other hand, at the line team level we feel there has been considerable success. Traditional professional barriers have fallen, and there is a general sense of interdisciplinary work that transcends uniprofessional, "guild" issues. The teams have functioned smoothly, as providers share in managing patients with demanding, complex psychosocial and medical problems. Just as importantly, the teams have served as important personal support systems as individual members face both professional and personal stress. Interpersonal conflict has been held to a minimum through group meetings encouraging patient-centered debate and rapid airing of conflict. Recently, in the medical unit, we have started an experimental team teaching program for medical, nursing, social work, law and administrative students. The BIAC teams, all of which serve as the faculty, have developed further cohesion through planning and conducting the course.

The teams meet weekly to discuss their patients and administrative problems faced by both the individual team and the larger program. No team leader is formally designated, and it has been clear that leadership functions have come more from force of personality than professional credentials. On several teams, the leadership role has been taken by nurses or social workers, not by the physician who has traditionally dominated in the medical model. As personnel turnover occurs, each team holds much of the responsibility for choosing the replacement for a member who has left. There has been remarkably little turnover, however, and it is hoped that team members view their role in BIAC as worthy of longterm commitment.

In addition to individual team meetings, periodic meetings of the entire interdisciplinary staff address both medical and administrative issues. Similarly, the individual "guilds"—physicians, nurses, social workers—meet as groups with their leaders who represent them on the BIAC core planning team.

It is the core team that has had the most complex history in BIAC as it moved from its initial planning function to its present role in monitoring the program and planning for the future. The internal function of such a multidisciplinary planning group, and even more importantly its relationship to the rest of the Hospital as a whole, remains complex, and we have yet to sort out some of the organizational implications.*

While BIAC was created as a distinct organizational unit within the Hospital, there was general agreement that it should remain closely linked to the traditional departmental lines. Yet, although overall Hospital objectives for outpatient care may share a common framework, it is clear that a primary care program comes into conflict with many institutional priorities. Moreover, the interdisciplinary professional relationships of such a program cut across hierarchical lines and pose further organizational dilemmas for our highly centralized physician and administrator dominated institution.

For example, with the BIAC Medical Director functioning as a unit chief within the Department of Medicine, he is accountable to the Physician-in-Chief and delegated the responsibility for monitoring the professional performance of the internist faculty, house staff and medical students in the BIAC medical unit. On the other hand, despite the fact that at present the Medical Director is an internist, he is also held *programmatically* accountable to the

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* Much of our thinking in the organizational analysis that follows has been aided immeasurably by Edna Homa, Ph.D. We owe her many thanks for her efforts in this area.

General Director of the Hospital for ambulatory activities in general obstetrics/gynecology. As such, he is given authority by the Hospital to act as at least coequal to the Obstetrician/Gynecologist-in-Chief in defining the BIAC practice *configuration* and *program*, while the Obstetrician/Gynecologist-in-Chief remains accountable for the *quality* of the obstetrical/gynecological care within the practice. When physicians are recruited, a new BIAC obstetrician, for example, would be sought and approved jointly by the BIAC Medical Director and the Obstetrician/Gynecologist-in-Chief.

For other members of the core staff, dual relationships and accountability also exist. Perhaps it has been the role of the Assistant Director of the Hospital for Ambulatory Services that brought into sharpest focus the conflicts posed by such an organizational model. He has until recently held responsibility both for the Hospital's general approach to ambulatory care and for the functioning of the BIAC practice. Thus he was expected to serve both as BIAC's advocate in negotiations with the Hospital, and as the Hospital's advocate in negotiating the terms of the practice. As we have outlined above and shall discuss further below, there are many issues which create stress in such a role. For example, what are the appropriate costs to be charged for space, general administrative services, etc.? In negotiating with those parts of the Hospital which provide services to BIAC patients, such as laboratory, radiology, patient registration, and billing, can one person effectively represent both the central administration of the Hospital and a primary care program? Additionally, in a Hospital offering ambulatory services which include specialty clinics, an emergency unit, subspecialty private practitioners, and outlying primary care centers, all of which compete for sharply limited space and resources, can a single administrator represent these needs and at the same time act as the advocate for a primary care practice? We have found that this does not work well.

Very similar conflicts exist for other BIAC leaders who find themselves frequently wrestling with issues of the practice needs versus priorities traditionally articulated by their parent departments.

With BIAC thereby representing a microcosm of the Hospital as a whole, the General Director has recently commissioned an evaluation to determine how best to define BIAC organizationally within the Hospital setting and how to clarify the role and operation of the multidisciplinary BIAC leadership. We have already made some decisions. The most important one is that BIAC will have its own practice administrator. The Assistant Director of the Hospital for Ambulatory Services will be responsible for administrative control of all Hospital-related ambulatory activities *other* than BIAC. The BIAC Practice Administrator will thus represent a new position at a level roughly equivalent to that of a Hospital assistant director.

We have also introduced some tentative changes in the BIAC planning group function. It is expected that virtually all the decisions relating to the program will be arrived at by consensus. While in this sense the planning group is conceived as a group of equals, to insure that a decision point is readily available if an impasse is reached, the BIAC Practice Administrator and Medical Director will share ultimate programmatic accountability for BIAC activities. They will therefore be empowered to break impasses and have the "final" word within the BIAC unit. We are also developing a formal avenue for adjudication and review if the decision arrived at by these two individuals is felt unjust or inappropriate by any one member of the planning team.

As implied by such an approach, although some details of the organizational relationship of the BIAC practice to the Hospital remain unclear, it is the authors' impression that partnership between the Medical Director and the BIAC Practice Administrator needs to be more formally established. These two individuals would then be held accountable by the Trustees and General Director for program operations and would be empowered to negotiate an explicit practice agreement with the Hospital. Such an agreement would clarify relationships to Hospital ancillary services, fiscal services, personnel practices, thereby refining and clearly defining the cost-revenue center that must serve as BIAC's foundation.

Such an organization would establish a degree of decentralization which has not been present in the past. It would, in effect, represent a compromise between two extremes: the first is for the program to remain within traditional departmental lines of the Hospital, the second is to opt for a separate department, or even corporation, with the attendant degree of autonomy that other institutions have chosen (16). We feel that the approach we have outlined above may represent a reasonable plan which can maximize the advantages of remaining within the Hospital framework, thereby preserving linkages and ties that have been rewarding for BIAC and the Hospital in the past.

IV. Problems and Prospects

With this somewhat detailed description of organizational problems and prospects, we turn now to a discussion of several unresolved questions which our program faces. We shall concentrate on areas relating primarily to establishing a primary care practice, teaching, and research program in the teaching hospital setting, leaving some more generic issues in primary care for discussion elsewhere in this symposium.

We feel that many of the problems we describe reflect the lack of a formal practice agreement with the Hospital. Negotiation of such an agreement in the next year should yield resolution of several of the issues we describe below.

A. *Financial and Marketing Issues*

For example, the determination of a fair "rental" charge is complex. What part of the intensive care unit that is open 24 hours a day should BIAC "pay" for? Probably little; but, on the other hand, should it not pay a premium for practicing in a setting replete with personnel and technology that can at times be very important to BIAC patients?

Consider the fees charged patients for laboratory work. Early in the BIAC experience it was clear that the turn-around time for laboratory work for outpatients was slow, in part due to competition with the pressing demands of the inpatient service. Further, the price charged patients was quite high when compared to the private practice marketplace. One way to receive adequate service appeared to lie in isolating such service to a degree, perhaps by contracting with an outside agency, a feasible project that many private practices and hospitals have used to good effect (17). When this was suggested, the Hospital argued that the relatively high fees charged were justified by third-party reimbursement conventions and by high fixed costs necessitated by institutional need for 24-hour service, quick response time, and an ability to do low volume, uncommon tests. Yet the discrepancy in fees when contrasted to the private office ($49 for a Hospital chest x-ray, compared to $20–$25) might serve in part to drive BIAC out of the competitive arena. Thus at the present time, if we decide to perform all laboratory work within the Hospital, we are considering establishing separate fees for in- and outpatient ancillary services.

There is a related problem. In part again because of third-party reimbursement conventions for ambulatory care, it is clear that many physicians use the office visit fee as a "loss leader" and marketing device, "profiting" from relatively low-cost, but high-fee services, such as electrocardiograms, and office laboratory tests (18). We have found that in order for BIAC to be competitive, it must gain some degree of financial "credit" for ancillary services. Otherwise the consequences may be higher visit fees, penalizing patients who choose to join the practice and making it again increasingly difficult to market the practice.

The fees charged, of course, may be related also to the amount of free care the practice provides. At the present time, BIAC fees are charged on a time basis, and are comparable to those in private internal medicine, obstetrics/gynecology, psychiatric, and social work practice in the Boston community (Table IV). They are also scaled according to the ability to pay, and the Hospital faces a 30% write-off rate for free care, partial payment, and bad debts. The Hospital has to decide periodically therefore what degree of free care it can afford to give consonant with third-party reimbursement formulas and the traditional charity mission of such institutions, and what "credit" to give BIAC for such institutional practice.

The revenue side has other complexities. The practice offers free care to Hospital employees, due in large part again to third-party reimbursement conventions. What "credit" should accrue to BIAC? In a different example,

TABLE IV

*Average Charge Per Visit ($)**

Before BIAC	1971–72	$15.25
BIAC	1972–73	15.50
	1973–74	18.50
	1974–75	21.25
	1975–76	22.00
	1976–77	23.25

* The charges represent weighted averages from the BIAC ob/gyn, medical, walk-in and mental health units. Ancillary charges are excluded. The relatively large increase in BIAC years 2 and 3 reflects a shift in visits from the walk-in unit to the more expensive continuing care team practice. The walk-in/continuing care ratio remained relatively constant in the 3 subsequent years. Figures cited are based on full charges and do not reflect fees scaled down according to ability to pay.

BIAC hospitalizes patients as private patients and as such generates inpatient revenue which in the past came to the "chief's fund" of a given clinical department. Debate persists between the practice and the Department of Medicine over control of this revenue; again, the manner in which such debates are resolved reflects institutional priorities. Whether or not the practice actually "breaks even" can only be fairly determined when all the other decisions concerning the allocation of appropriate and inappropriate costs and revenues have been made.

How a hospital-sponsored group practice is perceived by private staff physicians is a complex issue that many hospitals face. It has not proved generally difficult for our program; however, it may be increasingly so in the obstetrics/gynecology component. We have had good fortune in recruiting very capable obstetrician/gynecologists and midwives. At a time when women are asking increasingly for female health providers, and the midwives play a more important role in the uncomplicated delivery, the practice has come into fairly direct competition with the private staff. From the Hospital's point of view, with BIAC accounting for more than one-third of the obstetrical beds, growth of the practice has been encouraged, yet there has been concern from the private practitioners as BIAC attracts more middle and upper-middle class patients, drawing some away from our own private, part-time Hospital staff.

The use of new health practitioners, with social workers managing very difficult patients with the backup of BIAC's psychiatrists, and nurse-practitioners and midwives taking away part of the traditional role of the physician, has been a positive aspect of our program. Both patients and staff have shown a high degree of acceptance, and it is only in the "marketing" area in the internal medicine unit that there has been some difficulty. For example, if one decides to schedule a random new medical visit to a nurse-practitioner, marketing such an approach to patients who are not familiar with the capability of our practitioners becomes difficult. We have found that once the patient has contact with the nurse, no further problem ensues. At present, however, we limit first contact to the physicians (except in the walk-in unit and when a patient requests to see a nurse practitioner).

We also face the issue of charges. If one argues that, at least up to this point, midwives, nurse-practitioners, social workers, are paid less than physicians, one may reason similarly that the charge to the patient should be less. If, on the other hand, we are convinced that the quality of the service is comparable, one can then reasonably establish a policy of similar charges levied by all types of practitioners. In the past we have chosen to charge less for our new practitioners, but we expect to change this policy in the future. We still require careful study whether such practitioners do in fact represent a cost-saving trade-off and/or a qualitative improvement in care offered (19).

The question of introducing an incentive system that encourages high quality medical care in fee-for-service practice holds center stage in health policy debate today and cannot be discussed in detail here. In BIAC we have attempted to build in an ethic that rewards what we sense as appropriate. Financial incentive to hospitalize patients is minimal; the practice would at most gain very indirectly from excessive utilization of in-hospital beds or laboratory services, and peer review is built into the fabric of the program. However, we remain unclear about individual incentives—how to reward those who perform best, and how to stimulate those who could do more. The arguments range over various options and have been clearly articulated elsewhere.

Such debate is further complicated by the hospital-based nature of our practice. Can we within the standard personnel practice of our Hospital develop incentives for not only physicians, but also nurses and social workers who have traditionally been subject to one scale of pay across all institutional departmental lines? Can we indeed take the approach further and develop an incentive system for an entire team, including the secretaries and aides, as has been done quite successfully at another institution (20)?

While we are a fee-for-service practice, and as such do not have the "captive" population found in a prepaid program, the impact of our program on bed utilization may turn out to be quite striking. It is our impression that, for our Hospital, referrals to surgical services from BIAC may have increased. Patients are more carefully monitored and therefore turn to their primary physician when trouble supervenes, rather than seeking care at another hospital's emergency room. On the other hand, it appears quite clear that despite the growth of the practice, fewer patients are hospitalized on the medical wards than have come from the clinics in the past. The practice is busy, and patients tend to have complex medical illness, with the outpatient department attracting a disproportionate number of patients who have required hospitalization and those with such complex problems that they are sometimes sent away from private offices. Be that as it may, in a practice with five faculty internists and house officers both in the primary care and regular track, the number of BIAC patients on the medical wards seldom exceeds 10 to 15 and accounts for fewer than 8% of the annual admissions to the medical floors. This striking statistic, coming not from a health maintenance organization, but from a fee-for-service practice, points perhaps to one of the most exciting implications of our practice, when one views it in the context of public policy and attempts to contain cost. On the other hand, for a hospital that does not always have full beds, this can pose a problem in a day of increasing fiscal constraints.

Similar arguments may be applied to the emergency unit. We have been successful in moving many patients out of the emergency room into the BIAC walk-in and continuing care units. Emergency unit visits have decreased, and a greater percentage of the patients seen are admitted to a hospital bed, indicating that the population served is more appropriate for such an expensive, equipment and personnel-intensive unit. Costs are, however, relatively fixed in such a unit. While this trend should reflect better patient care, it probably has the net impact of costing the Hospital money, since the price charged and revenue generated in the walk-in unit is approximately one-quarter that yielded from managing the same patient in the emergency unit. Such realities indicate again that a hospital's willingness to support a primary care program must go sometimes well beyond traditional priorities.

B. *Referral Patterns*

In the setting of the academic health center, interaction between the primary care provider and the subspecialist may also prove difficult. In our Hospital there has never been considerable development of the ambulatory component of many of the medical and obstetrical/gynecological subspecialty clinics. As we noted above, at the beginning of the BIAC program many patients were seen in the subspecialty units by default. Over the years there has been gradual equilibration, with patients in the subspecialty units now more truly relevant to the given subspecialty. In terms of teaching and clinical research, it is of course important to have sufficient patients for the subspecialty unit.

Referral patterns from BIAC have, however, been variable and difficult to define. General internists in such a setting must have a wide degree of competence in order to maintain credibility as teachers at the medical school; in their role as patient advocates it becomes doubly difficult for them to refer every "interesting" patient to a subspecialist. Financial issues enter this debate, since referred patients may incur charges that they may not have had if they were not in teaching settings. From the point of view of the subspecialty unit, the revenue lost by lack of referral may impinge sharply on the viability of such a unit. It has been difficult to develop specific guidelines for referral, but it is clear that such efforts have to be undertaken. We and other groups are working on the competency-based nature of primary care practice, so that criteria for referral can be made more explicit.

C. *Patient Input*

Another area in which we have faltered is developing a formal means for patient input into the program. In the early stages of the program, a "consumer advocate" was hired, and a panel of BIAC patients was envisioned. The degree of governance that such a group should have was never worked out, however, and in its place a fairly good system for patient access to administrative personnel has developed. Periodic attempts to evaluate patient satisfaction have been undertaken, and it has been gratifying to see that the missed-appointment rate has fallen. The "cancellation rate" has risen, as patients have taken increasing responsibility for calling the practice when unable to keep an appointment. In addition, patient demands on the practice have increased as their expectations have risen. We still feel that we must develop a more formal mechanism, but how to do that in the setting of a complex institution, while giving more than token governance, remains unclear. The experience of the Genesee Health Service in Rochester, New York, points to some solution (21).

D. *The Academic Program*

The flux between the demands of teaching and patient care requires constant reevaluation and modification. Continuity of care, one of the stated prerequisites for adequate primary care, is clearly difficult. House staff must try to manage their patients, yet travel through varied ward and subspecialty areas, rural practices, and out-of-hospital rotations. The device of the umbrella team has been very useful, and rules limiting the house officers from attending BIAC on days in which they are admitting new patients to the Hospital have been helpful.

Continuity of care places similar demands on the BIAC faculty. In order to develop research and teaching programs, time away from the demands of practice must be assured. Again, team support and cross coverage have aided in assuring some degree of protected time, but the complex demands assailing faculty make this a difficulty more easily resolved on paper than in fact.

House staff have learned a great deal from the new health practitioners in our program. But there are problems also. The presence of midwives, for example, working in a program in which the number of deliveries is limited and in which the obstetrical house staff frequently feel that they might be more busy, comes into direct competition with some of the perceived needs of the house staff. The midwives have been successful in taking on roles as teachers, and in the labor suite they have begun to supervise deliveries managed by junior house staff and medical students.

In the Department of Medicine, with the advent of a faculty group practice, fewer and fewer patients arrive on inpatient wards without the care of a responsible primary physician. Thus, the ward house officer is less likely to "pick up" a new patient to follow thereafter, and it is traditionally such patients in which house officers have been most invested. We are attempting to become flexible in sharing patients, both on the wards and in the outpatient setting. But this effort to finally abolish the two-class system in-hospital requires that the BIAC faculty physician encourage increasing degrees of house staff responsibility, balanced by careful and constant monitoring.

E. *Physical Constraints*

We would be remiss if we did not note how the physical ambience and space affect a hospital-based ambulatory care program. Not only do the number and character of the examining and conference rooms help shape the setting, but perhaps even more important are the waiting areas, interview rooms for determining patient payment capabilities, and the halls leading to the patient care areas. In our own instance, Hospital space limitations impede our functioning optimally and now preclude expansion of the practice and teaching program. Here again, institutional resources and determination of priorities have a direct impact on the nature of the program.

V. On The Other Hand . . .

While we have concentrated on discussing some of the difficulties encountered by our program, it would be unfair to leave the reader with the impression that we feel time would be better spent in other areas. We are personally convinced that hospital-based primary care practice should and will serve as an important avenue for health care in the future, and that the rewards from practicing in and developing such programs far outweigh the problems encountered.

Practicing in a setting with the enormous resources of a hospital has strikingly positive attributes. Peer review is built-in; the faculty member who hospitalizes a poorly managed patient is subjected to harsh scrutiny as the unit medical record follows the patient upstairs. Opportunities for continuing education are almost overwhelming. The ease of integrating management of patients who require hospitalization or subspecialty referral must not be ignored. The rich expertise at all levels, clinical, administrative, and from the Board of Trustees is difficult to quantify, but should not be forgotten. While we have emphasized our sense of need for further decentralization for programs such as BIAC, we are also well aware that the parent institution takes by far the largest burden of risk for such a practice, particularly in the early stages of establishing its viability.

In terms of academic responsibility of such a program, the focal point for educating young health providers has been the Hospital, and providing role models in primary care in such a setting may be extremely important for attracting more students to such practice. We have some evidence for this already, as nearly one-half of the interns in the Department of Medicine applied to BIAC this year for the primary care residency track. Such a practice serves also as a potentially ideal laboratory for clinical and health services research; the results should serve to improve the nature of the practice itself.

While we sometimes look across the street with a longing glance and wonder if we would be better off physically and administratively removed from the parent institution, we have had an exceedingly exciting and positive experience, and we anticipate a similar sense for the future.

In this decade, more than one out of every four visits to a physician is to a hospital out-patient department or emergency unit (22). When last tabulated in 1973, 236,000,000 patient visits were made to such settings (23). As national entitlement draws slowly closer, these numbers will increase, no matter what arguments are propounded for the development of free-standing practices. If nothing else, programs such as ours must be developed further to bring equity to patients from all backgrounds and economic classes. The hospital serves as an important focal point for such issues, and our experience indicates they can be confronted head-on.

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Primary Care in a Municipal Hospital: A Case Study

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Introduction

For many years the medical care system in New York has been notable for its unusually extensive commitment to public hospital services. The existing network of 14 acute-care municipal hospitals operated by the New York City Health and Hospitals Corporation (HHC) is widely distributed throughout four of the five boroughs (Bronx, Brooklyn, Manhattan, and Queens). In recent years these hospitals have accounted for approximately one-half of all emergency room and hospital-based outpatient visits in New York. There are wide variations in the ambulatory and emergency care capabilities of these hospitals, as well as in the needs, demands, demographic characteristics and socioeconomic profiles of the various communities which they serve. Generalizations about this public hospital system are perilous. By and large, however, the municipal hospitals provide needed care to the poor, elderly, dependent, foreign-born, and otherwise socially dispossessed residents in New York. For example, Medicaid and Medicare enrollees now account for the great majority of public hospital ambulatory and emergency care visits.

These hospitals do not usually serve as a desirable and consciously chosen alternative to the private sector of medicine, but rather as a substitute and back-up system, helping to fill large gaps created by the skewed geographic distribution of private medical practice, financial barriers to care, and the difficulties of the total urban medical establishment in deploying its extensive, possibly unparalleled resources in a more flexible, creative, cost-effective, and socially equitable manner. Contractual agreements between the public hospitals and their voluntary hospital or medical school affiliates appear to have had relatively little impact in filling these gaps, in large part because of the extraordinary burden of responsibility for medical care that continues to be thrust on the underfunded and overworked public hospitals.

The municipal system faces many internal problems of its own: an unwieldy, lethargic, and unimaginative central management bureaucracy; difficulty attracting and retaining sufficient numbers of qualified and motivated professional staff; budgetary constraints compounded by the city's prolonged fiscal crisis; an unusually high proportion of foreign-trained medical house staff; and

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a general public image of the municipal hospitals as a "second-class" medical care system. Recently an increasing number of spokesmen, both from within and without, have argued that the municipal hospitals will be able to survive as an effective component of the New York City medical care system only if they can join, or can aggressively compete with, the private sector of medicine. Most of these arguments run along one of the following lines: 1) bring the fee-for-service private practice of medicine (both outpatient and inpatient) into the public hospital; 2) capture a larger segment of the medical care market by dramatic new large-scale financing arrangements (union plans, HMO's, prepaid capitation); 3) merge the public hospital and its voluntary hospital affiliate to create an amalgamated and expanded "public/private medical center" with a larger geographic and medical care need base. Without debating their specific merits, a major facet of all such proposals is the importance of decentralizing management and fiscal authority for public hospital operations so that each municipal hospital can define its mission, goals, objectives, strategies, and financial management plans and alternatives within a more discrete and controllable set of boundaries than now exists. For persons directly involved in the provision of ambulatory care in public hospitals, such a decentralization process has long been viewed as a crucial step in moving toward a clearer definition of institutional purpose and a more rational system of operational management and resource allocation.

Primary Care in Municipal Hospitals

No overall plan exists for the expected performance of New York's public hospitals in providing ambulatory and emergency care, and there has been no concerted effort to define, in operational terms, the subset of ambulatory care activities which could properly be regarded as primary care services. None of these hospitals, for example, has a primary care "track" within its medical or pediatric residency programs. Although all municipal hospitals are expected to have a "department" of ambulatory care, there is wide variation between hospitals as to the range of clinical services included in such a department, the organizational and budgetary arrangements for providing primary care, and the academic relationships between this department, other clinical departments in the same public hospital, and the related departments and disciplines at the affiliate institution. The organization of ambulatory care services at each public hospital is largely determined by factors such as local priorities and leadership, the internal dynamics of the particular hospital, the existing physical plant, the nature of the community being served, and the emphasis given to ambulatory care through the individual affiliation contact. In short, there is no clear and realistic set of guidelines or objectives for the provision of ambulatory care in the New York public hospital system.

It is important to underscore the fact that this so-called public hospital "system" is rooted in heterogeneity. While annual budgetary allocations among hospitals are made from a central pool of funds, and while there is a plethora of comparative HHC statistics ranking the various hospitals on a wide variety of performance characteristics, from the standpoint of ambulatory medical care delivery the total milieu and responsiveness of each hospital could as well be measured by the experience of a patient in making (or attempting to make) an unscheduled visit to the outpatient department (OPD). Can you be seen today? By whom? How long will you have to wait? Are interpreters available? Can you get an appointment for next week, or next month? Will you have "your own" physician? Will it be an attending physician or house officer? Will you see the same physician on successive visits? Can you make or cancel an appointment by telephone? How can you contact your physician between visits? Answers to these and other questions will be highly variable between the 14 public hospitals.

Primary care services are usually characterized by terms such as ease of access, continuity of the patient-provider relationship, and integration of general care and specialty management and consultations, both outpatient and inpatient. Against these normative features of desirable primary care must be placed the reality of OPD services in many of New York's public hospitals, where the predominant features are impersonality, long waiting times, multiple clinic referrals, frequent changes of physicians, no reliable access to a single "personal physician," and a general sense of being "lost in the system." Thus, paradoxically, while New York's public hospitals are providing primary care services on an enormous scale, they are generally not effectively organized for this important mission. There has certainly been little evidence of leadership or direction for primary care services from the central office of the HHC.

Ambulatory Care at Elmhurst

In 1973, a new Department of Ambulatory Care and Community Medicine was established at City Hospital Center at Elmhurst, a 900-bed acute-care public hospital in the western half of the Borough of Queens. In 1964, Elmhurst had entered into an affiliation agreement with The Mount Sinai Hospital in Manhattan, an affiliation later transferred to the new Mount Sinai School of Medicine. Elmhurst is officially designated as the public receiving hospital for a total service area of some 800,000 persons, and the services provided are those of a full-service acute-care general hospital (emergency room, OPD, ICU, CCU, renal dialysis, surgical subspecialties, etc.). Total emergency room visits at Elmhurst in the period 1973–1974 were over 100,000 per year, with total OPD visits of approximately 400,000 per year.

The new Department of Ambulatory Care and Community Medicine, academically linked to the Department of Community Medicine at Mount Sinai, was created by restructuring existing medical and surgical ambulatory care services. The Department of Medicine transferred to this new Department its budgetary and operational responsibility for the General Medical Clinic, Walk-In Clinic, Home Care Program, Methadone Maintenance Treatment Program, and Employee Health Service while the Department of Surgery transferred its budgetary and operational responsibility for the Emergency Unit. Total patient visits to these six clinical units in 1973–1974 were approximately 200,000 per year, or approximately 40% of all OPD and emergency room visits at Elmhurst.

The Department of Ambulatory Care and Community Medicine (DACCM) thus was basically designed to provide general ambulatory and emergency care to adult patients. Ambulatory and emergency pediatrics were not included, and except for the medical-surgical mix of activities in the Emergency Unit, the Department's various clinical activities were basically different facets of adult primary care as provided by general internists (1).

The Director of the DACCM was automatically a full member of the hospital's Medical Board and an organizational peer of all other Directors of Service. The DACCM budget of over $1 million, provided through the Mount Sinai affiliation contract, was used to support some 27 FTE physician positions as well as a limited number of nursing, administrative and other staff who were Mount Sinai employees. All other personnel working in the Department were employed by the HHC.

Of the Department's six clinical units, only two, the Emergency Unit and General Medical Clinic, were used for scheduled house staff assignments. The Emergency Unit had from three to six medical and surgical interns and/or residents on duty at different times during the day and night, with scheduled 24-hour attending physician coverage also provided on-site by internists and surgeons, varying from one to four attendings according to the time of day. The General Medical Clinic (25,000 visits per year) was basically staffed by paid attending physicians, with junior medical residents attending this clinic one half-day per week for brief periods during their medical ward rotations. The other four clinical units in the DACCM were not routinely used for house staff education, being staffed by attending physicians employed by the Department.

The Department was not a regular site for the clinical teaching of Mount Sinai medical students. However, many third-year students were assigned to the DACCM on a full-time basis during their required community medicine clerkships (2). No uniform policy existed regarding the participation of DACCM attending physicians in the teaching programs of other departments at Elmhurst or at the medical school, although all staff members held some type of medical school title.

Primary Care and Health Services Research

As a community-oriented public general hospital, Elmhurst's major activities were clearly identified as patient care and house staff training, in that order. For the DACCM, it was also important to undertake continuing efforts to improve the hospital's outpatient and emergency services by identification, analysis and resolution of selected problems in ambulatory care. Moreover, this commitment to quantitative ambulatory care problem-solving was consonant with the Department's role as an academic division of the Department of Community Medicine at the Mount Sinai School of Medicine.

In early 1975, a generous grant from the Commonwealth Fund made it possible to create a Health Services Research Unit (HSRU) within the Department. The HSRU consisting of a multidisciplinary group of professionals in the fields of operations research, medical sociology, biostatistics, patient education, public health, and clinical medicine, assumed major responsibility for applied research and community medicine education activities in the Department, addressing problems such as staffing patterns, waiting times and patient flow in the Emergency Unit (3, 4, 5), improved appointment systems (6, 7), needs and opportunities for patient education (8), and a variety of other issues related to resource allocation and improvements in the quality of ambulatory care (9, 10).

Unfortunately the establishment of the HSRU coincided in time with a period of sharply increasing fiscal cutbacks in the HHC, and many of the research team's efforts were necessarily focused on helping the Department to maintain the existing level of services in the face of ongoing budget reductions. Nevertheless, the existence of the HSRU exemplified the important principle of investing in applied research as a strategy for long-term improvement in ambulatory care. While no objective overall analysis of HSRU activities has yet been undertaken, it is generally acknowledged that the impact of the HSRU was timely and decidedly positive.

Primary Care in Public Hospitals: Some Major Issues

Much of the current literature on primary care reflects major concerns with two specific issues, the development of the primary care component of residency training programs and the creation of model primary care practices with an emphasis on multiprofessional teams. Clearly these were not the dominant concerns at Elmhurst during the period 1973–1976, not because they were considered irrelevant but rather because they were viewed as premature. The medical residency experience at Elmhurst was already strongly oriented toward general rather than subspecialty medicine. What this residency program lacked was a consistent and sustained emphasis on training for primary care in the ambulatory setting. Rapid development of this aspect of the residency program was definitely hampered by the fact that both the General Medical Clinic and Walk-In Clinic, the logical sites for primary care residency training, were not controlled by the Department of Medicine, thus requiring careful interdepartmental negotiations regarding any changes in the deployment of house staff, the content of their learning experiences, and any needs for additional faculty supervision and space. During the period 1973–1976, definite progress was made in better utilization of the DACCM as a site for medical house staff education, but educational opportunities in primary care could not be readily exploited. It must be noted, of course, that the severe fiscal constraints imposed on and by the HHC during these years directly impeded efforts to improve the organization and quality of house staff teaching programs.

As for the development of model interprofessional primary care practice settings, this again was a luxury rendered impossible by fiscal constraints. A cadre of six family nurse practitioners was developed by the Department in 1975, with assignments primarily to the Walk-In Clinic, General Medical Clinic, Home Care Program, and a number of other geriatric care areas. However, severe shortages of nurses and social workers and a total absence of health educators made it impossible to create stable new configurations of different health professionals acting as effective health care teams.

On the positive side, however, the delivery of primary care was clearly identified as a major and specific institutional mission. Moreover, the existence of the HSRU and a very good medical record system made it possible to study ambulatory care utilization patterns and to implement certain proposals for change. In addition, the fact that the DACCM did not depend primarily on house staff for the bulk of patient care activities made it possible to consider changes in primary care services without undue concern for the impact of such changes on residency training.

It appears likely that in all of New York's public hospitals there exist fertile opportunities for innovations in the delivery of primary care services and in the education of house staff in primary care. The apparent fiscal and administrative obstacles to such new programs are in fact an integral part of such new program development. They can never be ignored, but to some measure they can be overcome, modified, or incorporated. The New York City public hospitals represent a distinct challenge to innovators in primary care, with opportunities for major emphasis on new methods of resource allocation and for imaginative approaches to make inevitable trade-offs between costs, quality, and expected patient care outcomes.

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Primary Care in a Large Prepaid Group Practice

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Group Health Cooperative of Puget Sound is a member-owned health-care cooperative in Seattle, Washington, providing comprehensive medical care on a prepaid basis, with an enrollment of about 240,000 persons. This enrollment approximates the US population in age and sex characteristics (1). Currently in the Seattle metropolitan area one out of five households contains a Group Health member. Group Health delivers approximately one million outpatient visits per year, and approximately 20,000 hospitalizations per year with a length of stay substantially shorter than that of any area in the United States.

The service area for the prepaid group practice, the greater metropolitan area of Seattle, is about 50 miles long and about 20 miles wide. Within that area are the Cooperative's approximately 215,000 members.* Until 1977 the Cooperative had built one hospital to serve this population, a 315-bed hospital in the center of Seattle. In 1977 the Cooperative opened a new hospital in a suburban area directly east of Seattle, across Lake Washington, about 7 miles away. This apparently short move to the east is a long move from a functional standpoint, since Lake Washington divides Seattle from its eastward suburban neighbors. This new hospital has approximately 150 beds.

It is important to note that there is a difference between how many physical beds a prepaid practice hospital has and how many are staffed. At the time of opening of the new hospital the approximately 315 staffed beds at the Seattle hospital were cut back to approximately 240, while 85 beds were staffed at the new hospital to accomodate the members who were expected to shift a portion of their utilization to that hospital. This maneuver may give the reader some insight into the rather precise, but not painless planning that is possible in a prepaid group practice.

The hospitals are obviously not the front line in the primary care delivered by the Cooperative. The front line is composed of the primary care physicians' offices located throughout the area served. These offices are located in relatively small groups ranging from 7 to 18. It is essential to the Group Health notion of medical care delivery that the primary care offices be located as nearly as possible in the neighborhood of the members using them. Thus, the first "area clinic," consisting of about a dozen offices, was located in a local shopping center about 5 miles north of the original hospital and clinic. Built in the 1950s, it is a one-floor plan of relatively modest construction, corresponding to modest professional offices in similar surroundings across the United States. Each successive similar facility has been planned and executed with more

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* For the sake of simplicity we have excluded from this discussion 25,000 members who live and use facilities in Olympia, a town outside the Seattle area.

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amenities, until the last completed facility has a pleasing style and aspect decidely superior to that achieved in many professional offices. Like the physical amenities, the functional design of the clinics has evolved continuously. The most recent area clinics are arranged so that physicians practice in "clusters" of approximately 3 physicians along with 1 or 2 physician assistants, and an appropriate complement of nurses and receptionists. The entire clinic is composed of several such clusters and contains its own emergency laboratory, pharmacy, physical therapy and x-ray facilities. Nonurgent laboratory tests are sent to a central laboratory. At the present time there are 8 such area clinics strategically located throughout the metropolitan area.

Almost all primary care is produced in these area clinics by our present complement of approximately 100 family practitioners, 22 pediatricians, and 5 primary care internists, who associated with Group Health at a time when much primary care was delivered by internists. At this time an occasional internist applies to join the Group Health Medical Staff as a primary care physician. These physicians are welcomed as members of the Family Practice Section if they are willing to gain the necessary expertise to practice pediatrics, orthopedics, gynecology, prenatal, and other aspects of full family practice. The Internal Medicine Section itself, as a matter of policy, recruits only internists who wish to function as consultant subspecialists in hospital-based offices.

All the family practitioners practice in the area clinics, seeing their patients on rounds in the hospital. The area clinics have 6 to 12 family practitioners who function as a small group practice, the organization of which varies somewhat from clinic to clinic. For instance, in some clinics one of the group goes on rounds for all in rotation, while at other clinics individual physicians make their own rounds. In association with the 10 family practitioners in the area clinic there are 2 or 3 pediatricians. These pediatricians serve both as primary care practitioners and as consultants. Group Health members are free to choose between a pediatrician and a family practitioner for their children. Approximately 50% of the volume of pediatric primary care is delivered through pediatricians while the other 50% is delivered through family practitioners.

When a Group Health member has a health care problem, typically he or she will call the area clinic in which their personal physician practices, and typically their personal physician is a family practitioner. The physician's number as listed in the Seattle directory rings for the receptionist who works with their physician. If the patient is satisfied with an appointment as arranged by the receptionist the contact ends there. If, however, the patient wishes further advice or is not satisfied with the appointment as arranged by the receptionist, the nurse who works in conjunction with the physician will take the call. Finally, if further medical judgment is required in handling the problem by telephone the call will go to the physician. This sequence of events assumes that the patient indeed has a personal physician. Because there are constantly new members joining Group Health, frequently a member does not yet have a personal physician. In that case the area clinic will suggest a particular physician. The members are free to change their physician at will.

All the physicians function as a partnership, on a salary schedule approximately equal to the mean US physician's income, derived from a per capita amount prepaid by the membership. Because the individual physician's salary is not related to the services delivered nor the number of individuals cared for, there is no economic incentive for a physician to enlarge his practice. In the past it has been wryly observed that the physician who was especially competent, pleasing, and efficient was rewarded by attracting more patients and a resultant higher workload. After many discussions, in recent years a plan was struck upon to modify this situation. This plan is referred to as the "panel system." The patients who are committed to any particular physician are kept on record by an on-line computer. Typically a family practitioner who has a mature practice will have at this time from 1,700 to 2,000 patients who look to him or her as their physician. It is the feeling of the Family Practice Section that this number is too high to allow comprehensive family practice. Certain areas of practice, obstetrics for example, are sacrificed by many family practitioners in order to allow the panel size to remain this large. Were such sacrifices in practice not made, the panel size would be smaller.

Under the panel system the patients whom the physician cares for are identified and the continuing care of that panel is a defined and manageable responsibility, rather than an open-ended workload. Physicians who are efficient are rewarded by their own efficiency, and physicians who are especially pleasing to patients are rewarded by their patients' satisfaction, without undergoing an influx of more patients.

The computer program which manages the panel system is capable of identifying the number of patients cared for by a physician by age/sex distribution, how often they see their own personal physician, how often they are seen by other physicians whether because of "overflow" or by referral, how often they visit the Emergency Department, and so on. A computerized medical record system is being tested in one area clinic which will complement the panel system data. This medical record system, in addition to supplying a clear and accessible record, will allow the physician to scan the nature and frequency of the problems which he sees, and will facilitate clinical and health services research.

As alluded to above, in most area clinics a physician assistant, specifically a medex or nurse practitioner, is part of the "cluster." A physician assistant will typically relate to 3 physicians, helping them care for their panels of patients. This type of practitioner provides approximately 20% of all primary care visits at Group Health (2). Their practice is not governed by extensive protocols. Rather these physician assistants are expected to relate to the physicians with whom they practice as does a physician to any consultant. It is the practitioner's responsibility as a professional to know what he or she does and does not know and to seek appropriate help at all times. This arrangement has been markedly successful. Patient satisfaction with physician assistant practice has always been found to be high, and there is no significant negative pattern of physician or patient complaints that would indicate that the current system of physician assistant practice is problematic. Indeed the malpractice experience in the Group Health prepaid practice is such that claims are initiated less frequently per 1,000 population than in the United States as a whole, and less frequently than in Washington State.

Family practitioners at Group Health see an average of 22 patients in a day, average slightly under 1 patient in the hospital, and work an estimated 44-hour week. A family practitioner has available a full range of paramedical services including physical therapy, visiting nurse, occupational therapy, social workers and mental health professionals. In addition, the family practitioner has a roster of colleagues who are on-call in specialty and subspecialty areas. Each day the family practitioner can expect a particular general surgeon, orthopedist, neurosurgeon or neurologist, obstetrician/gynecologist, and so on, to respond to consultation needs. Ordinarily for pediatric consultation the family practitioner will ask the help of the pediatricians in the area clinic.

The 22-physician Pediatric Section conceives of itself as both a primary care and consultant group. The pediatricians feel that were they to become consultants only, the complicated problems that would become their steady diet might be oppressive. At the present time they deliver approximately 50% of pediatric primary care for Group Health and deliver 100% of consultations around difficult problems and difficult hospital admissions. Reflective of their philosophy, the pediatricians are located in the area clinics practicing side-by-side with the family practitioners. The Pediatric Section employs a few pediatric nurse practitioners who concentrate their practice in well-child care and minor medical illness.

The 22-physician Obstetrician/Gynecology Section has, until recently, been both a primary care and consultant group. In 1977, however, after multiple discussions with other members of the Medical Staff, the Section decided to become a consultant group only except for obstetrics and tubal ligations. Thus, a patient who wishes to see an Ob/Gyn consultant must be referred by a family practitioner or other physician within the group, except in the case of pregnancy or desire for a tubal ligation. True to the predominantly consultant nature of their practice, the Ob/Gyn physicians are not scattered among the area clinics but are located in hospital-based offices.

The Emergency Subsection of family practice constitutes an important part of primary care in the Group Health system. Until 8 years ago the Emergency Department was staffed by a rotation of family practitioners. At that time the Medical Staff decided that the nature of the problems encountered by emergency physicians could best be faced by a permanent group of career emergency physicians who could develop essential expertise in this area. A group of six emergency physicians was established to staff the Seattle hospital emergency department 24 hours a day, and in 1977 that group enlarged to a total of 11 in order to staff the new hospital. Approximately 17% of all hospital admissions are executed by these physicians. The sudden enlargement of the group by 5 physicians is a testimony to the value placed upon a smoothly functioning Emergency Department in the Group Health system, since the funding for these new positions must come from an overall closed-end, prepaid budget.

The two Emergency Departments in total see approximately 350 visits per 1,000 members per year. It can be reliably estimated that inclusion of out-of-plan emergency visits would not enlarge that number by more than 10–15%. Except for true emergencies, emergency utilization is discouraged at Group Health. An elaborate system has been worked out to implement that philosophy.

The first and most striking innovation in the Group Health emergency system was the establishment of the consulting nurse. A staff of consulting nurses, ranging from 1 to 4, depending on peak workload hours, is located in the hospital within the Emergency Department. It is the task of these nurses to help the Group Health member who calls with whatever health problem they may have. Calls may range from a complaint that one of the children has broken out in a rash, to a question of how to become associated with a personal physician, to a request for advice by a patient who has forgotten to take laxatives before a barium enema, to a call from a wife that her husband has suddenly been stricken by crushing chest pain. The chest pain complaint would trigger a call by the nurse to the Seattle Fire Department, which is capable of resuscitation and advanced life support. The other complaints would elicit direct telephone advice, possibly including advice to come to the Emergency Department. Occasionally the consulting nurse will telephone the appropriate specialist on-call for advice, or may step over to the Emergency Department for consultation with the Emergency Department physician. These consulting nurses handle approximately 120,000 calls per year for the system at large. The cost of approximately 60¢ per call we consider exceptionally low in view of the value of the service. Nurses recruited for this position are required to have had broad experience in medical, surgical and pediatric areas. Working in collaboration with the Medical Staff, they have elaborated a system of guidelines for a wide variety of health problems.

It is largely due to the consulting nurse system, operating in conjunction with the development of the "panel system," to which we attribute an unusual phenomenon: in contrast to the trend in the rest of the United States, the per capita number of emergency visits experienced by the Group Health population has declined in recent years. When a member does make an emergency visit, a record of that visit is on the personal physician's desk the next morning. For patients who are triaged away, the Emergency Department has the capability of advising their personal physician's nurse of the problem, and requesting that the nurse call the patient in this regard.

It is obvious that the original group of 6 emergency physicians, now 11, could not possibly handle the volume of 70,000–80,000 emergency visits experienced at the current level of Group Health enrollment. For this reason physician staffing in the Emergency Department is supplemented by a call schedule of family practitioners. In general, patients presenting in the Emergency Department are classified by the nurses and receptionists in attendance as belonging to a group which requires immediate and extensive medical attention, or those who, while their problem may be relatively urgent, do not require so immediate or extensive attention. This latter group is cared for by the family practitioners who share the call schedule. The former group is cared for by the full-time emergency physicians. The emergency group generally requires its physicians to function in any given emergency at the level of a specialist in that area. Thus, fracture reductions, curettage, chest tubes, cardioversion, intubations, and other elements of disposition, including the decision for admission, workup and orders, are all handled independently within the department under most circumstances. This high level of responsibility, together with a cooperative rather than economically competitive relationship with the rest of the Medical Staff, markedly enhances the practice of emergency medicine at Group Health. The emergency physicians and the family practitioners work in cooperation sharing both expertise and individual cases. It is interesting to note that the volume of workload presenting to family practitioners as they share emergency calls is in some measure inversely proportioned to the efficiency of their own practices in the area clinics. Thus, it has been in the family practitioners' own interest to develop the efficiency of the area clinics.

The Mental Health Service at Group Health should be considered an element of primary care, inasmuch as individuals may refer themselves to this service without prior referral of a physician. Such patients are initially interviewed by a psychiatric nurse who makes a judgment as to the most appropriate disposition. The Mental Health Service, composed of psychiatrists, psychologists, and social workers, is oriented toward keeping troubled members of Group Health functional through short-term intervention. Drug therapy, individual psychotherapy, group therapy, and referral to community resources are used depending upon the needs of the individual (3).

Like Mental Health, preventive care is an area that must be considered as a part of primary care. Since the inception of the organization in 1947 an emphasis on preventive care has been an explicit part of the principles of Group Health Cooperative. The elements of prevention within Group Health are not different from those practiced by physicians everywhere in the United States. Application of this ordinary preventive care, however, appears to have reached a high degree of penetration in the population. Recently Andy Shi, a medical student from the University of California at San Diego, followed a cohort of Group Health newborns during the first several years of life. The execution of the preventive schedule of well-baby checks and immunizations was completed on time for 98% of the babies studied. Executed by the University of Washington, another recent study (4) comparing pediatric preventive services delivered by Group Health physicians with those delivered by Seattle fee-for-service physicians to children of poor families indicated that Group Health physicians' delivery was substantially more complete.

Recently the Medical Staff began systematic organization of adult preventive care. This effort was undertaken largely at the initiative of the Group Health membership. The membership's elected representatives insisted in annual negotiations with the Medical Staff that an organized program of prevention be established. Previously the Pediatric Section had reviewed the literature extensively and initiated a systematic preventive schedule for children differing somewhat from that of the American Academy of Pediatrics. But in the less structured area of adult preventive care, no systematic schedule had been created. The Medical Staff was aware that the literature indicated there were no measurable benefits from the "annual physical," and therefore did not place a high priority on these examinations. The membership, under the influence of the wide publicity given the annual check-up tended like other Americans to seek such check-ups in the belief that they were especially useful. As a result a member who called in for a "annual physical" received an appointment 6–12 weeks in the future.

The discussion between the membership and the Medical Staff produced a Preventive Care Task Force composed of membership representatives, representatives of the Administration of the health care plan, and representatives of the Medical Staff. In July of 1975, after two years, of mutual education, the members of this task force were able to report that an organized adult preventive program had been begun under the direction of R. S. Thompson, M.D. First of all, the Medical Staff recognized that while the efficacy of preventive measures and preventive screening in the adult age group was not clear, a rational program to be updated consistently on the basis of the current literature was desirable. The starting point was a screening schedule based on a consensus of the Medical Staff regarding what was useful.

One of the 8 area clinics, with a population of about 12,000, was chosen as a trial site for innovations in preventive screening designed to reduce appointment waiting time. Nurse practitioners were chosen to assist with the screening. Based on the Kaiser Permanente experience, it was recognized that if the nurse practitioners did only screening, their jobs would become unpleasant. For this reason their work was scheduled to comprise about half primary care and half preventive screening. The program was successful in reducing the appointment waiting time to about one week. The effectiveness in disease prevention is yet to be assessed. It is interesting to note that the physicians in the trial area clinic found that these additional paraphysicians reduced the mixture of relatively simple cases in the physician's day, making the physician's workload uncomfortably complex. For this reason these physicians do not recommend that preventive screening be solely a paraphysician function in the future.

Representatives of the membership were anxious to extend the program to several other area clinics. The Executive Committee of the Medical Staff, on the other hand, recommended extension during the coming year to only one additional area clinic, recognizing that the analysis of the cost and benefit were incomplete and that modification of the proportion of paraphysicians involved in this work was probable.

The development of the adult preventive care schedule is an excellent example of the organic growth of Group Health Cooperative. The effort was instituted without a single outside dollar. The program has evolved through step-by-step negotiations without the large and sudden steps which outside funding often encourages, sometimes allowing the establishment of a program which must be later retrenched for political or financial reasons.

Having reviewed the delivery of primary care at Group Health, it may be helpful to review the genesis of the organization, and to describe its present special characteristics (5). The organization was born in 1947 from a small group of about 200 families who before and during the war had been interested in the concept of a cooperative designed to deliver prepaid health care. These founding members pooled their resources, purchased a small hospital and clinic in the Seattle area, and hired the physicians associated with that clinic as the first Medical Staff of Group Health Cooperative. Since then the Cooperative has grown into essentially a tripartite structure: the membership with its elected representatives and Board of Trustees; the Administrators who are hired by the Board to manage marketing, finances, nonpractitioner personnel, and facilities; and the Medical Staff with whom the membership contracts each year for physician services. Through the 1950s primary care was delivered predominantly by a multispecialty group. In the early 1960s however, several physicians endorsed the notion of a family practice group who would specifically be trained as generalists. And so the first family practitioners at Group Health Cooperative were brought into the medical group. In view of their success the Medical Staff and the Cooperative decided to start a family practice residency in the late 1960s, just before the advent of family practice residencies on the general scene. That accredited residency graduates four residents per year.

The governance of Group Health Cooperative, as may be apparent from some of the discussion above, is rather democratic and "congressional" in its personality. Decisions about medical practice itself are left to the Medical Staff by common agreement with the Cooperative. Decisions which pertain to medical care but are not part of medical practice itself, such as where new clinics will be opened and the nature of the new facilities, are made collaboratively through a number of different committees by representatives of the membership, the Administration and the Medical Staff. The Medical Staff itself is democratically organized, with each area clinic and specialty group, such as family practice, electing its own chief. Members from among these elected officers form the Executive Committee of the Medical Staff, presided over by the generally elected Chief of Staff. Each physician is ultimately responsible by contract to the Chief of Staff.

In describing the range of services which Group Health provides, it is easier to describe what is not covered than what is. As a policy of the membership, tranquilizers and vitamins are not covered. There is a $400 copayment for maternity services. Mental Health services are covered up to 10 visits per year, with a $7.50 charge per visit thereafter. Mental health hospitalization is not covered except by special contract with specific membership groups. Nursing home care itself is not provided, but all medical care associated with a stay in a nursing home is provided. All other aspects of medical care are covered, including all specialist and generalist office visits, the full range of hospitalization and surgery, drugs, laboratory services, physical therapy, occupational therapy, visiting nurse service, and special services such as that of the consulting nurse described above. Membership in Group Health Cooperative in 1977 cost about $35 per month for the individual and about $85 per month for a family of four.

An important element of the success of Group Health has been its ability to hold the per capita cost of medical care approximately 33% below the cost for the average American. As a result, a Group Health member receives the unusually broad range of coverage described above at or slightly below the monthly cost of an insurance policy delivering substantially less coverage. It is important to note that most of the savings realized by Group Health members emanate from lower hospital utilization. The per capita number of outpatient visits for Group Health members is the same as for the United States generally, and the per capita cost for outpatient services is the same as for the United States generally (1). Hospital utilization, on the other hand, is markedly reduced. Group Health members utilize about 450 bed-days per 1,000 members per year, while the United States generally utilizes about 1,200 bed-days per 1,000 population (1, 6). It is in this area of judicious and efficient use of hospitalization that the greatest challenge presents itself to the American medical community.

Group Health finds itself able to provide very well for the hospitalization needs of its members by providing approximately 1.5 beds per 1,000 members with some very small fluctuation dependent upon seasonal variations in morbidity. This bed requirement is in rather stark contrast to the United States' acute hospital bed supply of 4.5 per 1,000. These differences are not explained by any apparent demographic differences between the Group Health membership and the United States population. In order to explain how Group Health is able to do well on what would appear to be a limited bed supply, let me draw a scene which I have found instructive since my days at Mount Sinai.

Let us suppose that a 35-year-old man arrives in the evening in the Emergency Department with acute epigastric pain. I find that the patient's signs and symptoms and response to medication are compatible with those of peptic ulcer diasthesis with duodenal spasm. I believe that the patient's problem can be managed conveniently and effectively by his personal physician on an outpatient basis. I have no motivation, nor does the patient's personal physician, to hospitalize the patient. Similarly the patient, who is aware that all costs are covered by monthly prepayments, has no motivation to seek hospitalization. As a matter of fact, he would rather be treated at home. The hospital administrator who has a fixed prepaid budget for the year regardless of utilization, similarly has no interest in hospitalizing the patient. Even were hospital occupancy to dip to 50%, this would put the administrator's budget into the black, not into the red as it would in most fee-for-service hospitals. Although the Group Health Hospital occupancy rate actually hovers between 80–85%, the administrator has no reason to nervously eye any particular occupancy level as his "break-even point." Thus, neither the attending physician, nor the patient, nor the hospital administrator seek hospitalization; and the result is that the patient is appropriately treated on an outpatient basis.

When the hospital is full and cannot produce a bed for my patient, my professional ethics demand that I produce the best care at community standards. My recourse is simple. I telephone a fee-for-service colleague at any one of a number of Seattle hospitals, and ask him to accept the patient under his care. Group Health Cooperative is responsible for the bills thus generated since the care was deemed medically necessary by a member of the Medical Staff. This recourse is expensive, and that is why our hospital administrators see that the bed supply is adequate, and remain sensitive to the Medical Staff's perception of bed requirements. As an example of the delicacy of this balance, when Secretary Califano was calling for the United States to reduce its bed supply to 4.0 by the 1980's, our Medical Staff Executive Committee was urging that our current bed supply of 1.5 beds per 1,000 should be temporarily increased to 1.6 beds per 1,000 because of the inefficiencies and dislocations occasioned by opening a new hospital.

I have included this discussion of hospital utilization in the present paper because, although it is not directly descriptive of our primary care, it is a good example of the multiple negotiations, deliberations, and collaborative decisions that go into every building, policy, practice, and decision in a well-run prepaid practice. While I have not described these background elements regarding our primary care system, the reader should be aware that this complex process underlies the development of what I have described.

A final topic important relative to primary care at Group Health Cooperative is the quality of care afforded its members. It is important to note that epidemiologic methods may be used in a prepaid practice for quality assessment, but not in most health care systems since most do not have a defined population for which they are responsible. Thus, in investigating neonatal mortality we found that in 1972 the Group Health Cooperative per-population neonatal mortality was slightly below that of Sweden, which has the lowest national rate in the world (7). Similarly the maternal mortality at Group Health is remarkably low. We have done a series of studies in surgery which have a bearing on quality of care. We have demonstrated that Group Health general surgeons, in spite of having a surgical output (8) more than twice that of a comparable group of community surgeons in New York State, are able to devote more time to the patient both per outpatient visit and per impatient visit during rounds (9).

Even more interesting from a quality-of-care viewpoint was the general surgeons' experience in the treatment of appendicitis. Group Health surgeons performed appendectomy on the Group Health population one-third less frequently than did United States surgeons on the U.S. population at large. Yet, the death rate from appendicitis was two-third less than that of the United States at large (10). This analysis of appendectomy experience is basically epidemiologic, and can be performed only within a health care institution which has responsibility for a defined population. Much of this difference in surgery rate apparently has its genesis in the outpatient and primary care management of abdominal pain. This study suggests the possibilities of quality assessment in primary care in a prepaid practice such as Group Health Cooperative.

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Research Opportunities in Primary Care*

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Introduction

Primary care has become the shibboleth of the seventies. It is viewed as a potential cure for the secondary effects of maldistribution of medical resources, as a remedy for fragmented and/or duplicative care, and as a humanizing influence in an impersonal, technologic world. Specialization and the technologic imperative in medicine were accompanied by negative effects that initially were largely unrecognized and unexplored. The primary care approach is now expected to redress many of those ill effects, but it is being advocated with the same uncritical enthusiasm as were earlier technologic developments.

Pushing ahead with this newest panacea without a careful exploration of a number of basic issues clearly invites the same inefficiency and disappointment that has accompanied the technological revolution in medicine. To forestall such an eventuality, one must begin to examine the role of primary care in the provision of health services, whether different people (e.g., health professionals and consumers) have the same perception of this role, and whether primary care can be expected to accomplish the objectives it has apparently adopted. This paper focuses first on these fundamental questions and concludes with concrete examples of research that might be undertaken.

Fundamental Issues in Medicine and Primary Care

Scope of Medicine

Medicine faces an identity crisis today (1), in terms of establishing its scope and purpose in a new era of greater personal isolation, anxiety, and change and lower incidence of acute illness (2). Defining the scope of primary care is largely dependent on defining the nature of medicine, since many of the uncertainties about the role of medicine lie within the domain of primary care.

There is one inherent conflict in medicine today: whereas the intent of medicine is assumed to be the maximization of health, its orientation is basically on amelioration of disease. This conflict reflects the familiar split between the preventive and curative aspects of medicine, which has never been successfully bridged. It is, however, broader than that and concerns the question of whether the medical care spectrum should embrace the "positive" aspects of health. These aspects include such topics as improving interpersonal

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communication, developing better mechanisms for coping with stress and uncertainty, and eliminating self-destructive practices (e.g., abuse of tobacco, alcohol, narcotic drugs), as well as more radical approaches to health (such as parapsychology, holistic medicine, biofeedback, and sociobiology). Failure on the part of the entire field of medicine to deal with these issues directly will severely hinder developments in primary care.

Scope of Primary Care

The second issue is that of specifying the scope of primary care per se. Primary care tends to be described in terms of ideal functions and attributes —e.g., to serve as entry and referral point, provide a full range of basic health care services, provide support and comfort in times of health-related crises, and provide management and coordination of the entire health care process (3, 4, 5). Its main attributes have been described as "accessibility, comprehensiveness, coordination, continuity and accountability" (6). Primary care is expected to be comprehensive, coordinated, and continuous (from the provider's perspective) and convenient, compassionate, and competent (from the consumer's vantage point)—and to be attentive to cost as well (7).

This is a stunningly (some might say impossibly) broad mandate. Is it sensible, or even possible, to extend the scope of primary care further to deal with problems now assumed to be within the purview of other social institutions (such as loneliness and rejection of the aged, or poor self-image among minority children)? Shall primary care take over additional "health maintenance" activities as well? These will be major health concerns of the future. The primary care field must consciously decide whether to assume responsibility for them, not acquire them by default.

One problem in defining the scope of primary care is whether the field can provide "comprehensive, coordinated" medical services—all of which imply involvement of a variety of health professionals—at the same time it promotes greater self-reliance and individual responsibility for health-related behaviors. It is not clear that the same team of health professionals can treat illness effectively (a process that requires the patient to assume the sick role) and simultaneously help people develop their own capabilities to improve health status. Extension of primary care into previously "unmedicalized" areas threatens to exacerbate the "clinical, social, and cultural iatrogenesis" described by Illich (8).

The call for comprehensive and continuous care implies a volume of service that cannot be provided without increasing the costs of medical care. Primary care is not inherently "cheaper" than specialized care; neither is it likely to substitute for specialized care (9). To the degree that primary care tasks are undertaken by teams, each member of which generates demand for services, and to the degree that such services are additive rather than substitutive, medical care costs can be expected to rise.

These problems lead to the question of whether the benefits from primary care services outweigh the costs—in particular whether the marginal benefits are equal to the marginal costs. To address this question, one must not only assess the "value" (monetary or otherwise) of such services but also determine whose "value preferences" or standards are being used in that assessment.

The underlying questions are whether the presumed benefits of health care can be quantified, whether people can articulate the degree to which they value health, and whether they understand the economic and ethical implications of their value preferences (10). For example, do people value health more than other private or public goods and services (such as housing or national defense)? Do people value health to the extent that a given diagnosis should be made with an error rate of only 1 in 1000 rather than 10 in 1000 cases, or to the extent that a given disease should be cured 999 of 1000 rather than 900 of 1000 times? Do people value health services that support the sanctity of life more or less than those that support the quality of life?

The assertion that people can deal rationally and consistently with the task of placing a value on health is open to question. The "willingness-to-pay" approach to evaluating lifesaving programs, for example, has not gained wide acceptance; conceptual and methodologic problems with it persist (11, 12). Moreover, it seems clear that different people (e.g., of differing socio-economic status, or of varying health status) will value health (as opposed to other pursuits) differently and will value elements of health care differently as well.

Nonetheless, the problem of values is of more than passing interest to the primary care field. Resolution of this problem has implications for who should carry the bulk of the diagnostic and curative responsibilities in medicine; similarly, it has implications for the total costs of health care. To be more concrete, if primary care providers are assumed to arrive at a correct diagnosis in all but 10 of 1000 cases (or cure or successfully manage a disease in 900 of 1000), but the prevailing social value preferences are for a diagnostic error rate of only 1 of 1000 (or for a cure rate of 999 of 1000)—a level that might be attainable only by intensive, specialist-directed care—then emphasis on training and deploying primary care providers at the expense of specialists will be at odds with society's preferences. If prevailing value preferences are met (quite apart from the question of who meets them), the problem of exacerbating the rise in health care costs must then be confronted. Health policy decisions involving the costs and benefits of primary care should be society's decisions, not just the medical profession's; hence, revealed value preferences of society are important in defining dimensions of primary care.

At the level of the individual, another important reason for taking values into account is that the value of health relative to other personal, social, or national goals (e.g., inner harmony, education, or national defense) may be an important motivating or intervening factor in demand for health care, compliance with medical regimen, and other health-related behaviors (13). These relationships are poorly understood at the moment, but they are likely to have significant ramifications for primary care research in the future.

Cost-Effectiveness of Primary Care

The issue of whether professionals and/or consumers understand the implications of their value preferences—especially the "opportunity costs" notion that says, for example, that health dollars spent on specialist care are health dollars unavailable for other types of services—is rarely posed. One critical aspect of this issue is whether primary care, as a part of the medical care spectrum, is the most cost-effective way to deliver such services. For instance, the implicit assumption in current rhetoric about primary care is that its providers or teams are best suited to coordinate care or provide preventive services and health education, especially when compared to disease-specific hospital outpatient clinics or specialist physicians. Little attention has been given to the question of whether such functions could be as (or more) efficiently and effectively handled by other social agencies (e.g., schools, places of work), by as yet undefined public or private sector enterprises, or even by patient/computer interaction. That is, no one has carefully evaluated the cost-effectiveness of the implied centralization of many primary care tasks.

The issue of cost-effectiveness takes on added importance when the delivery of nontraditional services is contemplated, because of society's desire to insure services that fall within the scope of medicine, which in turn leads society to spend resources on services beyond what they would spend in the absence of insurance (14, 15). The impetus for better coverage of already accepted medical services (a problem for Medicare now) will undoubtedly be augmented by a campaign to insure new services (such as acupuncture or relaxation techniques). This will drive total medical care costs higher still. Under such circumstances, it is crucial to develop means by which the cost-effectiveness of primary care therapies such as those described above can be adequately assessed and monitored.

Role of the Primary Care Provider

Consideration of the scope of primary care is incomplete without explicit examination of the role of the primary care practitioner. Obviously, that role will vary greatly depending on whether the scope of primary care is taken to be broad or narrow. Current definitions of primary care clearly imply that the practitioner shall be a healer (of physical ailments), comforter (in times of mental or social stress), a manager/coordinator (of care for the "whole" family), and an educator (on such diverse subjects as sex, nutrition, and health habits). Expanding the scope of primary care obviously augments the role of the provider considerably—a role that already approaches Herculean proportions, at least in its ideal form.

Defining the role of primary care providers is difficult, because of the inherent conflict in attempting simultaneously to reduce fragmentation of medical care to fulfill the healer/comforter/manager/educator functions. One common suggestion is that this conflict can be overcome if primary care is handled by a "team" or in a group practice setting. It is not persuasive, however, to argue that dividing these functions among "team members" goes very far toward ending fragmentation in medical care, unless communication and cooperation among team members are extraordinarily high. Moreover, because of the potential stimulus to use of services as the supply of providers rises, division of labor within primary care is not necessarily consistent with the desire to reduce duplication of and inappropriate use of services. Research in primary care that does not consider these basic issues may be of little account, if not misleading, in the long run.

Quality of Primary Care

A final question involves the quality of primary care. Simply asserting that primary care will correct many of the ills now affecting medicine does not make it true. Numerous studies of quality of care document that basic diagnostic and therapeutic tasks—supposedly the areas that primary care would be best suited to handle—are performed at less than optimal levels (16). The mechanisms by which quality of the basic activities of medical care should be monitored are well understood in principle, but the means by which deficiencies can be precisely identified and corrected, especially in office settings, are much less well understood (17, 18). If primary care were to take on a broader role than it has at present—to include more humanistic, nontraditional, and extrabiological approaches to healing and positive health—current quality assurance programs may not be adequate. There is, furthermore, no inherent reason to believe that such services will automatically meet minimal quality of care standards. Thus, attention will need to be given to establishing the criteria by which future primary care activities will be judged and to implementing strategies for correcting deficiencies when they are discovered.

Summary

To reiterate, it seems necessary to make a much stronger effort to define the scope of medicine in general and to articulate whether medicine shall take on the broad assignment of promoting positive physical, social, and mental health. The primary care field must then stipulate where it fits within the scope of medicine; in particular, it must identify the boundaries beyond which it will not go with regard to more specialized medical services and the social services commonly held to be outside the domain of medicine. This includes articulation of the value preferences of providers and consumers with respect to health in general and to medical care components in particular. Establishing the cost-effectiveness of primary care providers (vis-à-vis other social agencies or the individual) in carrying out primary care tasks, and of different approaches to managing problems clearly within the primary care domain, must also be addressed. A clear definition of the role of the primary care provider is essential. Finally, standards by which the quality of traditional, innovative, and even radical primary care services can be judged need to be developed. The following discussion sets forth a series of research topics related to the issues formulated above.

Areas for Research in Primary Care

Scope of Primary Care

Numerous research topics can be suggested with respect to social and medical needs that can be anticipated in the future. One might start with the questions of how physical illnesses secondary to stress or mental and social dysfunction manifest themselves, and whether the incidence of such illnesses is rising. Research into areas as basic as development of disease taxonomies and classification systems takes on added importance in defining the scope of primary care (19)—i.e., what are the likely presenting "complaints" of tomorrow's patients and do these complaints fit into existing disease taxonomies?

Research is clearly needed to identify what concepts, methods, and techniques are emerging on the perimeters of traditional medicine. These may include both new and old quasi-medical techniques such as biofeedback or acupuncture (20). Research on how such techniques complement traditional medicine and how they present a challenge to traditional medicine needs to be carried out. For example, experiments in parapsychology may provide useful lessons for treating gastrointestinal or cardiac illness secondary to anxiety or stress. At all times, such inquiries should be subjected to the fair and impartial standards normally expected of controlled clinical trials within the medical field itself.

Preliminary research on the saliency of health indicates that health is the most important—or at least one of the four or five most important—goals shared by the American public (13). The empirical questions that need to be pursued in this area include: whether individuals value curing disease, avoiding illness, or promoting positive health; whether people value those three goals equally; whether they value such goals more than or less than other national or social goals; whether different persons place different values on health care goals; and whether they place the same values on them in periods of ill health and good health.

In investigating such questions, a number of conceptual or methods problems must be confronted, which themselves are fruitful research topics. For instance, it is not clear whether people make all or nothing judgments as to their preferences for good health as opposed to salvation or national defense, for example, or whether they are able to discriminate sufficiently to indicate marginal preferences. The latter is a crucial aspect of cost-benefit, cost-effectiveness, and willingness-to-pay concepts, and reflects the notion of trading off increments of education (or housing, or some other good or service) for increments of health. A related question is whether persons can discriminate among levels or types of health status that they prefer; to take an extreme case, do people prefer to invest in medical services directed at physical ailments rather than therapies for emotional problems?

Another important area for research concerns the role of individual health perceptions, such as a person's belief about his current and prior health status, susceptibility to illness, and anxiety about health (21, 22). If the boundaries of medicine or primary care are expanded, does this imply, as some have argued, that people will perceive themselves to be less healthy than before? Moreover, does it imply that people will be more likely to adopt the sick role, thereby further relinquishing control of and responsibility for health-related behavior to the medical profession? Answers to these questions are crucial, because research has shown that personal health perceptions play a significant role in the demand for medical services (21), especially primary care. Related areas of research include continued exploration of the relationship among sick role propensity, beliefs in the efficacy of medical care (to overcome illness) and of preventive care (to avoid illness in the first place), and beliefs about the locus of control (internal or external to the individual) over health-related events (23).

Cost-Effectiveness

The concept of cost-effectiveness assumes that one is attempting to minimize the total costs of a specified package of services (24). Little work of this type has been done in the primary care field. One potential area of research involves development of cost-effectiveness concepts and methods that can be understood and applied by clinicians and consumers.*

Cost-effectiveness methods could be applied in several research areas. For example, the cost of delivering medical services through primary care providers could be compared with the costs of delivering the same services either by nonprimary care medical personnel (e.g., specialists) or by nonmedical personnel (e.g., social workers, homemaker aides, or teachers). A second area might be the cost-effectiveness of different approaches to diagnosis or management of disease, such as, for example, procedures to confirm or disprove a diagnosis. For example, in cases of fever and sore throat, the costs of using an office visit as a screening device (to confirm a fever, establish presence of lymph nodes), followed by throat cultures and white-cell counts on a subset of patients in whom streptococcal infection is suspected, might be compared with the costs of obtaining laboratory work in all patients and seeing only those with positive cultures and/or high counts. The basic question, obviously, is whether it is more cost-effective to use the office visit or the laboratory procedure as the screening mechanism, assuming (which may not be appropriate) that the eventual outcomes (from either approach) will be the same.

The same general issue can be posed with respect to the humaneness or "art" of primary care. The question must be asked whether it is cost-effective to provide personalized, or individualized, "caring" services through the medium of primary medical care to persons who may need little medical care per se, but who may need a great deal of social and emotional support in times of stress or crisis. Research into nonmedical alternatives to meet some of these needs is called for, so that better-informed decisions can be made about the relative cost-effectiveness of the primary care approach to achieving positive health.

Finally, there are a number of traditional medical fields in which cost-effectiveness research is quite applicable. These include (to offer only a few examples) evaluation of alternative modes of disease prevention, of large-scale birth control and population planning efforts, of continuing medical education activities, and of team delivery of services.

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* We have not directly addressed the issue of cost-benefit analyses. With some modifications in the definition of terms, much of the cost-effectiveness discussion could be recast in cost-benefit terms. The analytic and conceptual problems become substantially more difficult to handle, however. In particular, the concept of "values" discussed earlier impinges much more on cost-benefit analyses than on cost-effectiveness assessments. Because the latter appear to be more readily understood and implemented in the primary care field, we have chosen to highlight them, but this should not mean that the cost-benefit approach as a research topic should be dismissed.

Role and Training of the Primary Care Provider

Much of the current research in the primary care field focuses on role and tasks of the primary care provider. This certainly includes development of new training programs, manpower studies, task analyses, curriculum evaluations, and the like—all directed at physicians, nurses, physicians' assistants, nurse practitioners, and a wide variety of other innovative paramedical personnel. Although such efforts are both necessary and worth continued effort, they suffer from several faults, which must be recognized and corrected.

First, they are often oriented toward an ideal concept of primary care in a frame of reference for the 1960s or 1970s, not the 1980s and 1990s (when most of today's trainees will do the bulk of their practicing). This is the health care equivalent of "planning for the last war" and is not a trivial problem. For this reason, evaluation of and planning for education and training programs must be made more sensitive to future needs.

Second, although much work in this area focuses on the types of medical personnel that should be produced and the relevant types of training programs, the need to assess the comparative returns to educational investments of this type has gained little recognition. The notion of trade-offs is relevant here, insofar as monies devoted to production of physicians is unavailable for production of nurses, social workers, or psychiatric counselors.

Third, there has been little examination of whether demand for a variety of primary care physicians truly exists, especially when other choices are available. For example, demand for primary care physicians can be artificially stimulated by the simple expedient of expanding such residencies and curtailing specialist residencies, but this does not ensure public (or professional) acceptance of primary care physicians for the wide variety of needs that they might be expected to meet. The long-run implications of such changes in graduate medical education need to be examined.

Fourth, there has been little exploration of whether the public and the medical profession believe that primary care functions reside in a single provider, a team, a group practice, or some as yet unspecified organizational arrangement. If this is not clarified, patient expectations about the primary care provider may be at odds with the provider's own expectations, with deleterious effects on both sides. Again, research into the meaning of "primary care" from the perspective of both consumer and provider is needed.

Quality of Primary Care

Research into the quality of primary care will continue to be an area of crucial importance. Such research will need to focus on three principal questions. The first involves the quality of care in traditional medical activities and concerns a number of familiar issues (17, 25, 26): how to establish standards (process and/or outcome) to measure quality of care; how to identify deficiencies in care; how to correct provider behavior associated with such deficiencies; how to monitor quality assurance efforts over time; and so forth. Although quality of medical care has been studied off and on for over a century, much conceptual and empirical work remains to be done, especially in the primary care area. In particular, methods for monitoring both the technical care and the art of care in primary care organizations need to be fielded (27). This includes specific work in measuring patient satisfaction with care (23).

The quality of care issues become considerably more complex and problematic as one contemplates the incorporation of radical and/or traditionally nonmedical approaches to health into primary care. Establishing process and outcome criteria in, say, psychiatry may be difficult enough; it becomes an overwhelming task in the parapsychology fields. Similarly, establishing criteria for assessing the quality of the use of known drugs (e.g., antihypertensives or antidepressants) is still a hard task (19); it is likely to be substantially more formidable in the case of drugs normally considered outside the medical armamentarium.

Third, explicit consideration must be given to the costs of achieving ever-better quality of care and whether they are balanced by eventual improvements in health. Mechanisms and organizations to assure the quality of care will be judged largely on the grounds of whether outcomes of such programs are worth the programmatic costs. To make such judgments, nationally applicable standards will need to be developed that indicate the incremental improvements in the quality of medical care that can be expected from the expenditure of different amounts of resources on, say, peer review. Ways of disseminating information about such cost/quality tradeoff issues need to be developed, so that the likely impact of quality assurance and peer review will be understood by providers and consumers alike. This is especially important because it is society's task, not the medical profession's, to decide "how much" quality improvement should be purchased with the nation's resources in the face of competing domestic needs.

Conclusion

This list of research problems does not closely reflect current research activities in medicine or primary care. The latter consist largely of attempts to find solutions to practical problems involved in implementing a health services delivery program or overcoming access or financial barriers to care. Although these solutions are clearly important in terms of making today's programs work more efficiently, they may well be insignificant in the long run. The critical questions at hand are whether primary care should grow, how fast and in what directions, and how to evaluate whether its growth has been successful. Some resources must be devoted now to asking these hard questions and finding ways to answer them, so that a decade or a generation from now the primary care field will not be regarded with the disappointment and cynicism that has been one of the legacies of the technical revolution in medicine.

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Primary Health Care in Less Developed Countries

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It is chastening but healthy for the United States to realize that we have much to learn from other countries in the organization of health services. This is especially true of primary health care which seems increasingly to be in a shambles in the United States. The vaunted advances of scientific medicine of which Americans have been proud has focused mostly on hospital inpatient care. Dissatisfaction with major gaps and deficiencies in primary care has led to appraisal of lessons to be learned from comparative analysis in various countries and situations. This paper summarizes some recent lessons from health care developments overseas with the hope that these lessons will be applied to the United States.

Issues to be Considered

Unit for Health Care

Physicians in the United States tend to congratulate themselves if they manage to broaden the range of their attention in health care to include the whole person. In family practice token attention is paid to the notion that physicians have responsibility to the whole family as a unit.

In less developed countries the sheer magnitude of the health care challenge forced physicians to begin to take responsibility for whole population units. Many countries around the world have moved toward the basic principle that health services should be regionalized with appropriate referral from peripheral primary care units to secondary and tertiary facilities. The peripheral primary care unit is expected to take responsibility for a defined geographical area or population unit within an established administrative pattern.

A number of interesting things happen when the community, rather than the individual, is considered the patient. This means that the health care team takes responsibility for the healthy as well as the sick. There needs to be much more tendency for the services to reach out centrifugally rather than waiting for patients to flow in centripetally. The services should take the initiative in setting up surveillance mechanisms to determine who is at risk in the population, to ensure appropriate preventive measures and to screen for early diagnoses and treatment. In defining health problems, a statistical or population-based approach permits a better understanding of dynamics. In the individual patient a woman will be diagnosed as pregnant or not pregnant whereas the community-patient is always about 4% pregnant. Similarly, it makes a great difference in how one thinks about the causation and control of a disease in the population. Awareness that epidemiologic variables can influence distribution sharpens diagnostic acumen and improves the use of community measures in control.

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Community-based health care requires the physician to begin to think like an economist. Regardless of how affluent the community is the reality must be faced that resources are limited relative to demand. For the community physician, judgments about cost-effectiveness must become reflexive. The distribution and allocation of health resources follows the dictum that the objective must be adequate care for all rather than unlimited care for the elite. Access to health services will be considered a human right. Determined efforts are required to achieve social justice and equity in coverage. Educational efforts should lead individuals to improve their health habits for the good of the whole group, rather than just to protect themselves.

Successful programs in several countries indicate that the new orientation described above is not vague and unreal. Under varied political and administrative systems a number of countries and projects have achieved a high level of success in implementing these goals.

Comprehensive and Integrated Care

Primary care should provide access to health services that are comprehensive in at least two dimensions. The old separation between curative and preventive services should be replaced by the recognition of a continuous spectrum of functions. The patient should receive attention as early as possible in the natural history of a health problem. This may require access to services ranging from the home to the primary care facility and on to secondary and tertiary care hospitals. A second dimension of comprehensiveness is in access to the skills and disciplines represented in the health care team. Care should be provided by those with appropriate expertise and this requires better mechanisms for screening to ensure that problems are channeled to the most appropriate care personnel.

In many programs which attempt to integrate public health and clinical care activities, a major problem is in how to relate single purpose categorical programs to general health services. It is often easier to organize a separate and focused activity devoted to a single component of health services such as control of an infectious disease or family planning. International agencies in the past often tended to impose such categorical disease control programs on less developed countries. Donors like to support activities in which objectives can be clearly definable and readily evaluated.

Abundant experience with mass campaigns in many countries has demonstrated to WHO. and other international agencies that caution must be exercised in promoting such categorical programs. Eventually, they have to be integrated into basic health services in order to maintain their effect. If basic services do not exist then the categorical activity will have to be maintained indefinitely at great expense. It now is generally agreed that the overall integrated service must always be the ultimate goal. Specific categorical programs may be promoted for a while as special emphases if viewed as part of a process of phased introduction of a sequence of activities. This is most relevant when an activity has been neglected and there is a gap in overall services. In many less developed countries particular efforts are being made now to integrate basic delivery systems for health, nutrition and family planning.

Reallocation of Roles in the Health Team

Some of the most interesting innovations in primary health care have been in developing new categories of health manpower. To have primary health care done mostly by middle level health practitioners rather than doctors is clearly more cost-effective than a purely doctor-based service. There is increasing evidence that the quality of care provided by health auxiliaries is just as good as that provided by doctors or perhaps better. Auxiliaries and middle level personnel can be trained to carry out routine tasks systematically and with much precision. Physicians tend to be distracted by looking for rare conditions and therefore are less likely to concentrate on the conditions with the highest statistical probability of occurrence. Although they may identify and treat the rare conditions somewhat more rapidly, it also means that many more patients are subjected to unnecessary tests and therapeutic procedures. Adequate care can be achieved by nondoctors by building in definite rules for rapid referral of conditions which can be specified according to defined criteria just as readily as the care of common ailments. Modern advances in diagnosis and treatment actually simplify many health care functions so that they do not need to be performed by doctors, but physicians continue to exercise their monopoly largely for historical and financial reasons.

Field studies in many countries have shown that with appropriate training and supervision, auxiliaries can readily take care of 85% to 90% of primary care problems. In a health care system where auxiliaries take care of routine problems, doctors can extend their capabilities to provide health care coverage to as many as 20,000 to 40,000 population. Since the more difficult and complicated cases will be referred to them, their clinical responsibilities will be more interesting and challenging. They have the further challenge of learning how to cope with community problems and the organization of preventive services.

New approaches have been developed in allocating responsibilities to the various members of the health team. The fundamental principle is to delegate downward in the system all activities to the minimum level where they can be capably handled. This leads to major changes in traditional patterns of practice.

Once roles are reallocated, then there should naturally follow an intensive retraining of each category of personnel. Much has been learned about making practical training more efficient. It is not true, for instance, that a great deal of repetition is required to learn routine tasks. In a working environment where the relevance of particular tasks is immediately evident, routines can be quickly learned.

Community Participation

Much lipservice is given to promoting community involvement in health planning but little is done about promoting the use of the people themselves as a major resource. In many situations as health services have become more efficient they have inadvertently weakened the capacity of communities to solve their own health problems. Just as in psychiatry, there is great danger in primary care when the provider of services creates dependency among the people who are being helped. The mystique of the medical profession has always included a tendency to project an image of omniscience. In training patients to turn their worries over to doctors, we have made them feel that they cannot understand their own health problems.

A new horizon in research is to discover new ways of working at the interface between the services and the community. A new approach to education directed to mothers increases the potential for solving health problems at the earliest possible stages. This will not happen spontaneously because both health personnel and the public give greater priority to treating advanced cases of illness where relief of suffering seems more dramatic.

Conclusions

Renewed interest in Washington in international health has emerged from recognition that a greater emphasis on health in foreign assistance might change the image of the US as the major arms merchant of the world. There is a reaffirmation in both the White House and Congress of humanitarian concerns.

This potential for increased funding comes at a time when we have much more to offer technically than ever before. We do not need to continue to make past mistakes through which US influence distorted the health services in many countries by promoting an inappropriate emphasis on specialized hospital care, high technology and an unnecessary scientism in medical education. As a result of careful field research over the past two decades, we can make it clear that we are not recommending a lesser quality of health care for poor countries. The best care is what meets the needs of most of the people of a country. There are many countries where 60% to 70% of the total health budget has gone into running the medical school and teaching hospital.

The new developments in primary care that have come out of international experience have relevance for the United States. Many of the leaders who are working out innovative health care systems for the United States learned the new approaches while working in poor countries.

We have learned that we have no right to send health professionals as advisors to other countries. Even as consultants we have less and less to offer. We are, instead, entering an era of mutual collaboration in technical cooperation. Through long-term relationships between institutions and professionals in more developed and less developed countries new approaches to research and training can be developed. Both countries will profit from what is learned.

Cross-cultural experience provides an objectivity which helps in seeing new relationships and opportunities. Overseas service leads individuals to see problems and potential solutions in their home situation that they would never have noticed before gaining their new insights. For those who develop the necessary expertise there are increasing opportunities for periods of work overseas interspersed with continuing involvement in their home environment.

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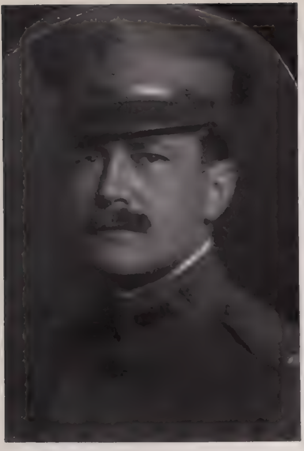

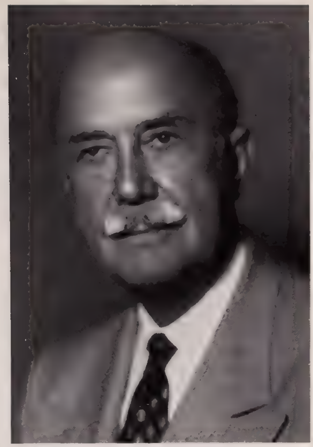

IN MEMORIAM
George A. Baehr, M.D.

The death of Dr. George Baehr at the age of ninety-one ends the unique and remarkable career of a commanding figure. As a physician for some 70 years, he was a lasting influence on The Mount Sinai Hospital and Mount Sinai School of Medicine, as well as local, national and, indeed, international medicine. It is customary to include one photograph in an obituary; but we have chosen to show two, thus illustrating two roles he played at almost opposite ends of his career. The first picture shows the handsome, debonair, assured, 31-year-old commanding officer of Base Hospital 3, the Mount Sinai unit of World War I. The second shows the austere, elegant, elder statesman at the peak of his career, devoted to the broad socioeconomic aspects of the delivery of medical care.

Always precocious Dr. Baehr attended DeWitt Clinton High School, Columbia University, and then graduated from the College of Physicians and Surgeons at the age of 21. After completing a rotating internship at Mount Sinai, he served as house surgeon to Dr. Arpad Gerster, one of the pioneers in precise and aseptic surgery. Originally Dr. Baehr had planned a career in internal medicine with the goal of becoming what was then termed a "diagnostician." But with typical long-sighted acuity, he realized that the prestige, teaching, and training in surgery at that time far surpassed what was available in medicine.

Dr. Baehr moved so effortlessly from one sphere of activity to the next that to describe him in any one role denies the breadth of his daily activities. Yet his devotion to clinical investigation and bedside medicine proved to be the springboard of his exceptional career. After graduation from the house staff, he acquired the scientific disciplines of the day and by 1914 was named chief of the infant pathology department. His researches in bacterial endocarditis, focal nephritis, and collagen disease remain classics. In 1919, he helped establish the clinicopathologic conference format, an educational exercise still used as a basic component of medical school education. Throughout the years, generations of young physicians were enriched by the profound clinical insights of his bedside rounds.

His interests in the broader community aspects of medicine were first evidenced when he joined a Red Cross commission to the Balkans in 1914 to help combat at first hand a devastating epidemic of typhus fever. Many years later, he inaugurated a consultation service at Mount Sinai that was devised to provide modern techniques of diagnosis to the community at modest cost. As Mayor LaGuardia's close friend and confidant, he planned and then served as first president of the Health Insurance Plan (HIP). This service still provides comprehensive sound medical care at modest cost for almost one million city employees. Because of this service to his community, Dr. Baehr was awarded the Sedgewick Memorial Medal, the Herman Biggs Memorial Medal, and the Distinguished New Yorker Medal. Additionally, he served as President of the New York Academy of Medicine, as consultant to the Surgeon General of the United States, as a member of New York City Board of Hospitals for 25 years, and as a member of the State Public Health Council for 35 years.

His capacity as an administrator and leader emerged when at the age of 31, he assumed command at Base Hospital #3. There, he organized the prompt and expert care of thousands of young men wounded in the Battle of Château-Thierry during the Meuse-Argonne offensive. From 1928–1951, he served both as chief of the Medical Service and as Physician to The Mount Sinai Hospital. As an administrator, his alert mind grasped the facts quickly, appraised the alternatives from every point of view, and then reacted with prompt and appropriate decision. His service ran smoothly; there was no room for carelessness, sloth or negligence.

Perhaps most unique in his role as a leader was his vision and his capacity to prepare for the future. For example, as he judged the scientific revolution in medicine after the World War II, he announced to a startled voluntary staff that Mount Sinai was embarking on developing a full time faculty. He realized that each department would need a nucleus of full-time people to serve as teachers and investigators of the new advances in medicine. This decision actually proved to be the first stirrings of Mount Sinai School of Medicine.

Paralleling his concern for the future was his devotion to outstanding young physicians. He constantly sought financial support so that his best students could develop the techniques for future leadership. More than money, however, his steadfast support of aspiring and talented young physicians launched many careers. Perhaps the single outstanding tribute to Dr. George Baehr are the literally hundreds of exceptional investigators, clinicians, and medical leaders whose first stimulus came from his example. In his senior years, he maintained his devotion to Mount Sinai by continuing to offer his name and prestige, sage counsel and indefatigable effort.

One may wonder what qualities enable a man artfully to combine so many discrete careers. Were they his remarkable astuteness and intellect, his incisive judgment and vision, or his energy, his courage, his assured confidence? During one of his favorite activities, he may have answered the question best. Once as he and his beloved Francine glided smoothly across the Roseland Dance Floor, Dr. Baehr whispered, "When the music changes to a waltz, don't keep dancing the fox-trot."

LESTER R. TUCHMAN, M.D.
and
MARVIN F. LEVITT, M.D.

Immunoreactive Epidermal Growth Factor in Human Amniotic Fluid

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EDWARD W. GRESIK, PH. D., AND THOMAS KERENYI, M.D.

Epidermal growth factor (EGF), isolated from the submandibular gland of male mouse, is a single-chain polypeptide of 6045 daltons (1). Human epidermal growth factor (hEGF), which is probably identical to urogastrone and is structurally and immunologically related to mouse EGF, has been purified from urine (2–5). It has been estimated that urine may contain up to 40 μg/liter of urogastrone (6). Human saliva and milk also contain EGF in concentrations of 5.6–16.8 ng/ml and 80 ng/ml, respectively (7). By using a heterologous radioimmunoassay with hEGF as reference standard and radioiodinated tracer and antibodies raised against mouse EGF, Starkey and Orth could not detect EGF in human amniotic fluid obtained at the time of delivery (7). Because of the potentially great importance of EGF in development, we wish to provide evidence for its presence in human amniotic fluid obtained by amniocentesis.

Methods

Radioimmunoassay for EGF: Amniotic fluid was centrifuged at 10,000 rpm for 10 min. The supernatant was decanted and was concentrated by membrane filtration (Amicon Diaflow UM 2 membrane) to 1/10 or less of the original volume. The concentrated amniotic fluid was assayed for EGF by the radioimmunoassay method of Barthe et al with minor modification (8). The same method was used to assay the unconcentrated amniotic fluids and chromatographic fractions. EGF, used as reference standard, tracer, and antigen to raise antibodies in rabbits, was prepared from submandibular glands of male mice by the method of Savage and Cohen (9). The EGF was homogeneous on polyacrylamide gel disc electrophoresis and gave a single precipitation line by the Ouchterlony technique with the antisera raised in our laboratory (Fig. 1) (10). The EGF also gave a single precipitation line with two additional antisera raised independently against purified EGF preparations, confirming the purity of the EGF used in the present study (Fig. 2). EGF was iodinated by the chloramine-T method. ^{125}I-EGF was separated on a Sephadex G25 gel column and was stored at −30 C. The labeled EGF was purified prior to the assays by

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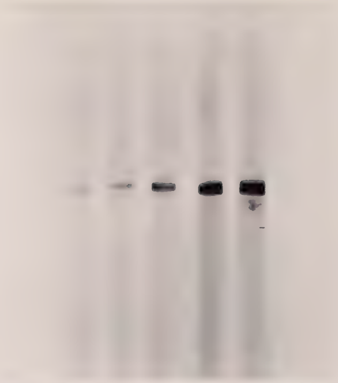

FIG. 1. Disc electrophoresis of purified EGF. Samples of 10, 20, 30, 40 and 50 μg of protein were applied and the electrophoresis was carried out at 2.5 mA/tube. The gels were stained with Amidoblack and destained electrophoretically.

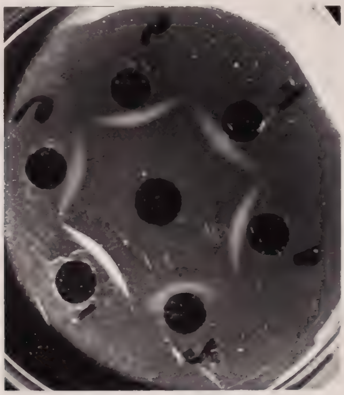

FIG. 2. Immunodiffusion of purified EGF against rabbit anti-EGF antisera. The central well contained EGF and the peripheral wells contained antisera raised in rabbits against EGF preparations purified independently in 3 laboratories. Well 1: antiserum A: well 2: antiserum B: wells 3–6: antiserum C. In these studies antiserum B was used.

gel exclusion chromatography on Sephadex G50 gel column. In the radioimmunoassay procedure the incubation mixture (0.5 ml) consisted of 0.2 ml standard EGF (0.03–4 ng) or the unknown, and 0.3 ml of antiserum diluted appropriately (about 1:100,000 final dilution) to bind approximately 50% of the trace ^{125}I-EGF (10,000 cpm). The mixtures were incubated for 3 days at 4 C, after which 50 μl horse serum and 0.8 ml 20% polyethylene glycol (Carbowax 6000), in 0.05 M phosphate buffer, pH 7.5, were added to separate the bound and free EGF after centrifugation for 20 min. at 7000 rpm. The precipitates, which contained the bound ^{125}I-EGF, were counted in a Beckman gamma scintillation spectrometer. In this assay the logit B/Bo was linearly related to the logdose and was used to calculate the amount of EGF on a computer.

Chromatography of Amniotic Fluid and ^{125}I-EGF on Sephacryl S-200 sf Gel

The amniotic fluid was lyophilized, dissolved in water (1/10 of original volume) and dialyzed at room temperature against 100 volumes of 0.15 M NaCl containing 0.025% sodium azide. 1–2 ml of concentrated-dialyzed amniotic fluid was chromatographed on a 41 × 1 cm Sephacryl S-200 sf (Pharmacia) gel column. The column was packed and washed according to the instruction of the manufacturer. Elution was with 0.05 M phosphate buffer, pH 7.5, at a downward flowrate of 18 ml/hr. 0.3 ml fractions were collected and assayed directly for EGF. The same column and conditions were employed for the chromatography of ^{125}I-EGF. To 1 ml of 0.05 M phosphate buffer, containing 0.5 mg cytochrome C, 0.5 mg bacitracin and 0.1 g of sucrose ^{125}I-EGF (approx. 380,000 cpm) was added and the mixture was chromatographed. The eluant was monitored at 280 nm and 0.3 ml fractions were collected for counting.

Results

By using a radioimmunoassay with purified mouse EGF as reference standard and radioiodinated tracer and antisera raised against mouse EGF we have analyzed a series of 31 amniotic fluids for EGF. The range of EGF in 28 amniotic fluids, obtained at 16–24 weeks of gestation, was 0.06–1.1 ng/ml, with a mean of 0.25 ± 0.23 ng/ml. Much higher levels, 26.7, 3.6 and 2.4 ng/ml of EGF, were found in repeated assays at different dilutions in three amniotic fluids, obtained from a 15 year, 34 year, and 21 year old woman, respectively. In all three cases with high EGF levels the pregnancy was terminated at 23rd-24th week. In none of these cases was there any indication of complications of pregnancy, genetic disorders, or obvious abnormalities of the conceptus.

Although the EGF radioimmunoassay used allowed for a minimum of about 10 pg per assay tube, the assay was not considered reliable below 30 pg per assay tube. Since several amniotic fluid samples were in this low range, amniotic fluids were concentrated by membrane-filtration or by lyophilization for further analysis of the immunoreactive EGF. Within the range of assay the concentration of EGF and the volume of the concentrated amniotic fluid were linearly related (Fig. 3). Furthermore, the competitive binding curves for highly purified EGF and amniotic fluid were parallel, suggesting that the amniotic fluid contains EGF or EGF-like material (Fig. 4).

The lyophilized amniotic fluid was dissolved in water and dialyzed against 0.15 M NaCl containing 0.025% sodium azide. When dialyzed amniotic fluid was then chromatographed on a Sephacryl S-200 sf column and the fractions were assayed directly for EGF, the average elution volume for the immuno-

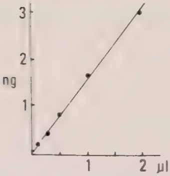

FIG. 3. Relationship between volume and concentration of immunoreactive EGF in concentrated amniotic fluid. Amniotic fluid was concentrated by membrane filtration and assayed for EGF as described in Methods.

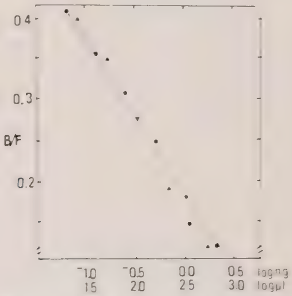

FIG. 4. Competitive binding curves for highly purified standard EGF and amniotic fluid. The bound-to-free (B/F) ratios are plotted as a function of logng of standard EGF (filled circles) or logμl of concentrated amniotic fluid (triangles). The amniotic fluid was centrifuged, concentrated by membrane filtration, and used for the competitive binding in the radioimmunoassay.

reactive EGF was similar to that of ^{125}I-EGF (Fig. 5.). Essentially similar results were obtained by using Sephadex G50 or G75 gels. However, since it permitted high flow rates, Sephacryl was preferred. The chromatographic separations of three amniotic fluid samples gave comparable results. The dialyzed amniotic fluid was stable at 4 C with respect to its EGF content and gave reproducible results on repeated chromatographic separations.

Discussion

Our findings indicate that human amniotic fluid, at least between 16–24 weeks of gestation, contains EGF or EGF-like material which crossreacts with mouse EGF. The radioimmunoassay, however, provided no information on the actual concentration of EGF in the amniotic fluid, since in this assay mouse and not human EGF was used as the tracer, reference standard, and antigen. This assay is, however, specific for EGF, and antisera raised against EGF do not crossreact with a number of known polypeptide hormones, including hGH, hTSH, hFSH, hLH, hCG, hACTH, prolactin, gastrin, insulin, glucagon, bradykinin, or angiotensin I (6, 7), some of which may occur in amniotic fluids.

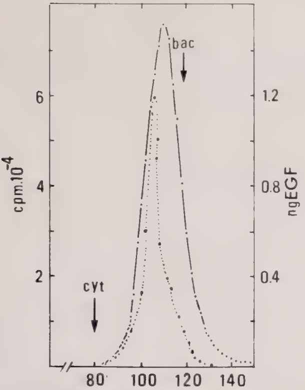

FIG. 5. Chromatography of amniotic fluid and ^{125}I-EGF on Sephacryl S-200 sf gel. Concentrated amniotic fluid was chromatographed and the fractions assayed for EGF or radioactivity as described in Methods. Abscissa: number of fractions. Ordinate: cpm/fraction or ng EGF/fraction. Cyt=cytochrome (MW: 12,750); bac=bacitracin (MW: 1410).

Competitive binding assays and chromatographic separation of the immunoreactive material provided further support for the presence of EGF in the amniotic fluid.

Although the physiologic role of EGF is not known, several of its biological effects have been well documented. In general, it enhances keratinization and the growth of epithelial cells and fibroblasts in vivo and in vitro (11–13). In addition, it inhibits gastric acid secretion (14, 15). Because of its demonstrated effects on proliferating and differentiating cell systems, the presence of EGF in the amniotic fluid is intriguing. Fluctuations in the level of amniotic fluid EGF may correlate with stages of development and may have as yet unknown diagnostic significance. Of interest is a recent report that EGF stimulates the secretion of chorionic gonadotropin by cultured human choriocarcinoma cells (16).

Summary

Human amniotic fluids, obtained by amniocentesis at 16–24 weeks of gestation, were analyzed for epidermal growth factor (EGF) by using a heterologous radioimmunoassay. The range of EGF in 28 amniotic fluids was 0.06–1 ng/ml. Much higher levels of EGF up to 26 ng/ml, were detected in 3 amniotic fluids. Competitive binding assays and chromatography of concentrated amniotic fluids provided additional evidence for the presence of immunoreactive EGF in amniotic fluid.

Acknowledgment

We are indebted to Drs. D. Krieger and R. Revoltella for the antisera (A, C).

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Control of Perinatal Group B Streptococcal Sepsis: Efficacy of Single Injection of Aqueous Penicillin at Birth

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BRUCE A. HANNA, PH.D.

Abstract

Early onset Group B (GBS) streptococcal disease results from systemic invasion by GBS following superficial contamination from the mother's birth canal. Its clinical course is often fulminating beginning shortly after birth and causing several thousand deaths annually in the USA. Therapy begun after diagnosis is often unavailing, with a mortality rate of 50%. *Control of the disease therefore depends upon prompt preventive measures.* Attempts to eradicate the maternal carrier state of GBS by using antibiotics gives erratic results and is ineffective. Active immunization of mothers with vaccines has been suggested as a possible approach; this is an area for continued study which offers no applicable preventive modality at present.

At The Mount Sinai Medical Center's hospitals, a single intramuscular injection of 50,000 units of aqueous penicillin given at birth *in the delivery room* to all live-born babies avoids early onset invasive GBS disease. External contamination is not affected. Systemic protection is due to the plasma penicillin levels; all strains of GBS have a low minimal inhibitory concentration (MIC). More than 130,000 deliveries have been so managed since 1952. Prospective controlled trials of this method conducted in a number of geographically separated obstetrical centers are urgently recommended.

Introduction

Streptococcus agalactiae, the group B hemolytic streptococcus (GBS) has become an extremely important pathogen in the neonatal period, estimated to cause 5 to 6 thousand newborn deaths annually in the USA. The disease is currently reported from many other countries.

There are two clinically and epidemiologically distinct forms of GBS disease in the neonatal period:

A. Early onset (perinatal) disease: symptoms begin within a few hours up to several days of life. Septicemia, respiratory distress, periodic apnea and shock may come on abruptly; the mortality rate is 50%. These infants are infected with the same subtype of GBS as can usually be cultured from the asymptomatic mothers' vagina, urethra or rectum. There are 5 GBS subtypes (Ia, b, c; II and III) any of which may cause early onset disease; all strains studied are penicillin sensitive.

B. Late onset GBS disease: this clinical disorder becomes evident some ten days up to ten weeks or more after birth. Septicemia occurs with or without purulent meningitis, osteomyelitis, or soft tissue abscesses. The GBS subtype involved need not be that carried in the mother's birth canal. Late onset GBS disease is outside of the scope of this report.

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GBS can be cultured from the vagina, urethra, perineum, and rectum from a varying percentage of women and from the urethra of their male consorts. Unlike some genitally transmitted infections, the women and men here concerned are almost always asymptomatic. Vaginal cultures of 499 nonpregnant asymptomatic college women demonstrated a GBS carriage rate of 20% (1). Reported vaginal carrier rates vary from time to time, from place to place and depend on the use of selective culture media. Thus, comparative study of vaginal cultures for GBS revealed 9.5% positive with blood agar plates, 25% with selective plate medium and 36.8% using a selective broth medium (2).

Serious GBS disease in neonates is a fairly recent phenomenon but the organism has long been known to colonize the birth canal of asymptomatic parturients (3). Passage of the newborn through the birth canal of an asymptomatic mother harboring GBS may result in: a brief surface contamination; asymptomatic colonization of some duration at several cutaneous and mucosal sites; systemic invasion with septicemia resulting in disease. It is this condition which can be suppressed, in our experience, by the timely use of penicillin.

Etiological Factors

Lancefield serological grouping of hemolytic streptococci into groups A, B, C, and so on, derives from different surface carbohydrates (4). The five GBS subtypes are in turn distinguishable by their containing five other separate carbohydrates (types Ia, b, c, II and III).

There are numerous microbe-host interactions in which many persons are colonized with only few diseased. The disparity between infection and GBS disease is not often explicable. It is clear that some babies are at increased risk of invasive disease because of the following: prolonged rupture of the membranes, premature birth, and babies small for gestational age. Babies at risk for these reasons constitute two-thirds of fatal cases of early onset GBS disease, but normal healthy full term babies constitute fully one third of cases. (5) Some mothers during labor may be quantitatively more heavily colonized yet fully asymptomatic—the concept of the "dangerous carrier" so well established for Group A streptococcal respiratory carriers.

For systemic invasive early onset GBS disease to occur there must be an inoculum of organisms sufficient to overcome body defenses, i.e., phagocytic capacity and the presence of antibacterial inhibiting substances in plasma and tissues. These substances may be type-specific antibodies delivered transplacentally or antibiotics capable of bactericidal effect against all five GBS types. GBS strains studied are susceptible to penicillin; the median minimal inhibitory concentration (MIC) of 244 GBS strains was 0.05 μg/ml of penicillin (6).

As with other microbial agents a strain of GBS may retain its serologic classification but change in other characteristics such as virulence. As long ago as 1934 Lancefield reported loss of certain properties without change in serologic specificity in a GBS strain. (7) A property such as virulence can conceivably emerge or decline as a result of ecologic or evolutionary changes. The relatively recent emergence of invasive neonatal GBS disease suggests such a development. This is different from an "inherent age factor" exemplified by Coxsackie viruses invasive only in suckling mice. In a bacteriologic study of 188 strains of GBS collected prior to 1938 Brown reported without comment that three came from infants. (8) At that time and in succeeding decades neonatal septicemia due to Group A streptococci was well recognized but it was only in 1958 that Nyhan and Fousek first drew attention to the distinctive fulminant clinical picture of non-group A streptococcal neonatal sepsis. (9) Since then there has occurred an ever increasing incidence of GBS noenatal disease in many parts of the world (5). One is led to suspect that a virulence factor(s) specific for newborn hosts has been emerging.

Prospects for the Prevention of Early Onset Neonatal GBS Disease

It is well recognized that while many newborns at birth are colonized with maternal GBS, few develop GBS septicemia and its complications. It is estimated that of 100 colonized mothers at least one baby will suffer invasive disease. But which baby? *All babies should be considered at risk.* At present there is no certain method of predicting freedom from risk.

Early onset GBS disease strikes quickly often with little warning, with periodic apnea seen earlier than in respiratory distress syndrome and with irreversible shock. Specific antibiotic treatment, even when begun "early" often proves unavailing. The abrupt onset of irreversible shock such as one associates with Gram-negative sepsis, is not easily halted. There is some suggestion that the cell wall of certain strains of GBS possess the ingredients for displaying endotoxin effects (10). Although seldom emphasized, Kim and Watson reported certain Group A streptococcal strains showing an enhancing effect on trace amounts of endotoxin (11). The classical approaches to prevention include *environmental measures, immunization procedures* and *chemoprophylactic measures.*

Environmental Measures

GBS appears to have found a safe permanent haven in the birth canal and anal canal of women and may have so evolved from its bovine reservoir. An interesting comment reported in 1934 stated "that they are derived from infected milk and pass from the anus to the genital tract would seem to be likely, but evidence for such a source is not yet available" (3). It is very likely that anorectal colonization is a major source of contamination of the perineum and explains why more positive cultures are obtained from the urethra and vagina than from the cervix. Permanent and consistent eradication of GBS from the colonized rectum has proved to be almost impossible with presently available methods.

Can GBS be effectively driven out of the birth canal with antiseptics? While this possibility has again been raised recently (12), it is not very likely to be effective. Colebrook and Maxted applied mercurochrome, undiluted dettol, crystal violet, brilliant green and 10% dettol paste to the external uterine os and the whole vagina on admission to hospital, three and 24 hours later. Failure was accompanied by (ital theirs) *"species believed to be of little or no pathogenicity were replaced or joined by other species of definitely greater pathogenicity, e.g., B coli, B proteus, hemolytic staphylococcus and fecal streptococcus"* (13).

Can GBS be safely, effectively and consistently driven out of the birth canal by the systemic administration of penicillin to which GBS is highly susceptible? It had been hoped that one could eliminate the risk to babies by identifying mothers with positive genital cultures early in pregnancy, and eradicate the organism by administration of penicillin or ampicillin. Unfortunately, the experience has been to the contrary (14, 15).

A recent careful longitudinal study of 382 women followed through pregnancy, delivery; and the puerperium showed that for GBS genital carriage, some were chronic carriers, some transient, some intermittent. Some of the patients received antibiotics during pregnancy for intercurrent illness with no observable influence on the prevalence of GBS carriage rates (16). The erratic nature of the vaginal carrier state in pregnancy adds to the despair in attempting to control neonatal disease by antibiotic prophylaxis in mothers (17). Consistent eradication of GBS from maternal mucosal surfaces cannot be relied upon, despite the susceptibility of the organism to penicillin. Indeed, babies treated with penicillin for invasive systemic GBS disease may continue to excrete the organism in their stools for many weeks. The condition is similar to the pharyngeal carrier of N. meningitidis in whom penicillin does not eliminate the carrier state despite the in vitro susceptibility of the organism. *At this time it is necessary to conclude that a reliable method for the environmental control of maternal colonization for the prevention of early onset GBS disease is not at hand.*

Immunologic Measures

Homologous type-specific rabbit antisera have been demonstrated to protect mice against challenge with some strains of GBS (18, 19). Are there supporting data from human immunological research which give rise to optimism for the control of early onset GBS disease? Artificial active immunization with vaccines given to prospective mothers has been proposed. It is reasonable to believe that it would be useful to have GBS type specific antibody (preferably all five types) in the serum of a newborn at risk of septicemia, provided such antibody is indeed protective in character and of sufficient titer. Baker et al reported higher median type III antibody level in 43 mothers of healthy infants than in 29 mothers of infants with type III disease (20, 21). These observations were made with a radioimmunoassay (RIA) test in which the antigen employed was not type specific. This test apparently measures a variety of antibodies (precipitins, agglutinins, opsonins). Nevertheless these results are suggestive of some potential role for type specific antibody in the resolution or prevention of invasive disease in the newborn. However, Wilkinson's recent report of the effect of GBS antibody is less optimistic: "no evidence was found in this study for type-specific protective antibody in infants. To the contrary, infants with group B type III meningitis or septicemia had approximately the same mean antibody concentrations as did those colonized with type III but were not ill" (22). In several sets of twins no appreciable differences in antibody concentration were observed with sera of the twin with fatal GBS *disease* versus the twin who was merely colonized.

It is often assumed that there is equivalence between the level of maternal antibody and that of cord blood. One of us has reported large disparities between maternal and umbilical cord levels of neutralizing antibody to poliovirus (48 pairs) and Coxsackie B viruses (102 pairs) (23, 24). A recent report of maternal-cord serum pairs tested with GBS type Ia showed seven maternal sera protective, but four of the corresponding cord sera were not. The authors stated "our results indicate that the presence of maternal antibody cannot invariably be relied upon to provide protection of the human newborn infant against GBBH streptococcal infection" (25).

With regard to the possible effectiveness of antibody (not in prevention but in therapy) there is a recent report of the influence of fresh blood transfusion in neonates. In that report, 15 babies had early onset GBS sepsis (7 type III, 4 type II, 2 type Ia and 2 untypable.) In brief, nine of the babies received blood later determined to have opsonic antibody against their infecting strains and all survived. Of the other six patients receiving fresh whole blood which did not contain opsonic activity, three died. The authors found that to be effective, donor blood should be given in a volume greater than 40% of the baby's blood volume (26).

At this time it must be concluded that presently available immunologic data cannot predict consistently which newborns are at risk, nor provide means for effective mass control of early onset GBS disease. Continued immunologic studies, however, are essential for the development of better understanding of the host-organism interactions in humans.

Control by Intramuscular Injections of Penicillin at Birth

Delivery of babies from maternal GBS carriers frequently results in colonization of the neonate. Entry of the organism into the systemic circulation will occur in some, perhaps resulting from inhalation, ingestion, or other means. The initiation of disease depends partly on inoculum size, virulence of the strain and partly on the baby's host defenses, i.e. the ability of leucocytes to ingest and to digest the GBS, and perhaps the presence of type specific functionally active opsonic antibody received via transplacental transfer. These events, however, are not predictable.

Fortunately all GBS strains examined, regardless of serotype, are susceptible to penicillin. There has been no change in this regard during the past 2 decades (27). The intramuscular injection of 25,000 units/kg of penicillin results in peak serum concentrations of 22–25 μg/ml one half to one hour after administration (28). Serum concentrations of penicillin are dependent on plasma clearance rates; accordingly, the infants considered most vulnerable to invasive early onset disease (premature infants and those small for gestational age) exhibit higher and more durable plasma levels of penicillin.

Prevention of Early Onset GBS Disease at Mount Sinai

At the Mount Sinai Hospital since 1952 (and since 1964 at Elmhurst Hospital) all live born infants have been routinely given an intramuscular injection of aqueous penicillin G at birth in the delivery room. This does not interfere with customary delivery room activities. This routine was initiated for the prevention of ophthalmia neonatorum, as had been used elswhere. (29) More than 130,000 infants have been managed in this way. We are not aware of any other hospitals utilizing this practice at present.

During the past decade personal communications and an abundant literature made clear that the incidence of fulminant invasive neonatal GBS disease was a problem in nurseries in many parts of the world. However, our institutions seemed to be spared such patients, although GBS colonization was observed. A preliminary letter, published in 1975, indicated the apparent absence of such disease which we, ascribed to the influence of the penicillin given within 2–3 minutes of delivery. (30)

Is it reasonable to consider that the dose of penicillin and the timing of its administration are *ample reason* for our fortunate serendipitous observations? The matter of dose in relation to the low minimal inhibitory concentration (MIC) has been discussed above. The *time* of administration may be equally important in providing an anti-streptococcal barrier at a point when any circulating organisms are beginning to multiply. In an animal model introduced for the study of streptococcal endocarditis; it was observed that antibiotics can *prevent* endocarditis "*if given within a half hour of intravenous injection of the bacteria, and that if delayed for 6 hours treatment failure occurs despite continuous intravenous infusion*" (31). This is not unlike the problem of early onset neonatal GBS disease: prevention is what must be emphasized, for treatment is often ineffective.

Allergic reactions to the parenteral use of penicillin in the early newborn period has not been documented, unlike the variable incidence in older children and adults. Furthermore, this single intramuscular injection while effective for the purpose given, does not result in supra-infection from Gram-negative organisms.

It is always necessary to consider that observer error (clinical or bacteriologic) may have occurred on occasion at our institutions. When one introduces a method with a specific aim in mind, observer bias becomes more likely. In this case, an ongoing routine originated for another purpose was observed to have another important beneficial effect.

It is unlikely that our experience would differ so markedly from that of neighboring institutions on the basis of bias or of chance. A recent informal survey of a number of neonatologists in several New York Hospitals kindly conducted by Dr. Lipsitz (32) indicates that in 1977 of 32,218 deliveries there were 27 cases of early onset GBS disease with 12 deaths, i.e., 0.84 per thousand live births. Reported attack rates for early onset GBS disease vary widely from one to as high as 3 per thousand live births. The mortality rate among cases is approximately 50%.

At this time the intramuscular injection of penicillin at birth appears to be highly effective in preventing the development of invasive GBS disease in the early perinatal period.

Discussion

Streptococci serologically identified as Lancefield group B are recognized in animals, notably in bovines in whom it has been an important cause of mastitis. Whether GBS cultured from humans evolved from the bovine species is moot; opinions are sharply divided. There are biochemical and other differences among the group B streptococcus.

For at least fifty years GBS has been found in the birth canal of asymptomatic parturient women. It is quite possible that the primary nidus is in the rectum as was much earlier suspected (3) and seems likely from a recent study (33). Despite the widespread existence of GBS colonization, it has been, and remains, an infrequent cause of disease in pregnancy and the puerperium. Although neonatal disease due to this family of organisms (5 serotypes of GBS) is recorded as early as 1938, disease has been rare until fairly recently, and is now reported from many countries. It is generally believed that of each 100 mothers silently colonized at least one baby will suffer invasive systemic disease; many more will be contaminated or colonized. Various reports indicate that of each 1,000 live births one infant is likely to have invasive disease 50% of whom will succumb despite antibiotic therapy begun after the disease is suspected.

At present it is not possible to predict which baby will sicken or die of early onset GBS disease. It has been shown one of twins may die, while the other be asymptomatically colonized. As full-term babies are vulnerable, all should be protected.

A recent abstract described the successful prophylactic use of penicillin (50,000 to 100,000 units/kg/day) for infants less than 2500 grams at birth, continued for at least 48 hours and up to 10 days if GBS was cultured from any site. As full-term babies were excluded from that regimen, seven developed GBS septicemia including a 3620 gram baby who sickened at 40 hours of age and died (34). Our experience suggests that such large and continued doses of penicillin may not be necessary and that full-term babies also need protection from GBS septicemia.

Neither environmental control nor immunologic methods presently available assure prevention of early onset GBS disease. The method of intramuscular administration of 50,000 units of aqueous penicillin to all newborns at birth appears to be effective. In order to confirm or reject these results, controlled trials in a number of geographically separated areas are needed in which care is taken that penicillin is administered within a few minutes after birth.

Summary

Early onset neonatal group B streptococcal disease claims thousands of lives annually in the USA alone and is being reported from many other countries.

The organism has been known for many years to be part of the genital and anorectal bacterial flora of women. The relative recency of its capacity to produce overwhelming invasive disease of newborns suggests an evolutionary change in virulence specifically for newborns; there has been no substantial change in the limited frequency of disease in adults.

Newborns at special risk are those with prolonged rupture of the membranes and those who are either premature or small for gestational age. One third of cases occur in healthy full-term babies. All babies are potentially at risk. Indeed, there have been twin births in which one died of overwhelming septicemia while the other was merely colonized externally. The onset of disease is often so swift and fulminating that even so-called early treatment is of no avail. *Prevention is the only way to avoid these thousands of deaths.*

The prospects of various proposed modes of prevention are discussed in this report. Evnironmental control is not effective. Control by successful active immunization of pregnant women or passive immunization at birth with type specific antibody is a matter for additional study but offers no applicable solution at present. It has been observed at The Mount Sinai Medical Center Hospitals that the intramuscular injection of 50,000 units of aqueous penicillin to all newborns upon delivery has apparently affected control of early onset GBS disease. This routine has been in use since 1952, does not interfere with usual delivery room activity and is not accompanied by untoward effects. More than 130,000 newborns have been so managed. Allergic reactions to parenteral aqueous penicillin given in the early newborn period have not been documented. The single intramuscular dose of 50,000 units of aqueous penicillin does not result in suprainfections due to Gram-negative organisms. The babies may be colonized on various sites but blood stream invasion is controlled by the plasma penicillin levels confronting invading GBS, all of which have a low minimal inhibitory concentration (MIC).

We wish to encourage prospective controlled trials of the method as specifically described.

Acknowledgment

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Fatal Poliomyelitis with Recovery of Virus from Cerebrospinal Fluid

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Abstract

The first known case of paralytic poliomyelitis to occur in New York City since 1972 is described. The patient gave a history of immunizations with the inactivated poliovirus (Salk) vaccine. The diagnosis was made by isolation of poliovirus type 1 from cerebrospinal fluid. The virus was classified as a wildtype. The source of the infection is not known.

Introduction

Poliomyelitis was once an important health problem in the United States. After the introduction of the inactivated poliovirus (Salk) vaccine in 1955 and oral live poliovirus (Sabin) vaccine in 1961, there was a dramatic decrease in the number of clinical cases reported. We report a fatal case of poliomyelitis, the first in New York City since 1972, in whom the diagnosis was established by recovery of poliovirus type 1 from cerebrospinal fluid.

Case Report

A 34-year old Caucasian female psychologist was admitted to The Mount Sinai Hospital on October 22, 1977 with weakness in her legs. Three weeks before admission, she had coryza and mild sore throat which she recovered completely. Three days before admission, the patient developed headache and discomfort in her back, shoulders and neck. The next morning she experienced nausea, vomiting, and fever to 103°F, followed within 24 hours by weakness of both legs, for which she was admitted to the hospital. The patient was not taking any medications, had no exposure to animals, had not traveled recently outside the New York area, and had not been immunized recently. To the best of her knowledge, none of her personal contacts were ill. She had received three injections of inactivated polio vaccine as a child.

Physical examination revealed an alert and intelligent young woman. Vital signs were normal except for rectal temperature of 103°F. Neurologic examination showed flaccid paralysis of both lower extremities, with proximal musculature weaker than distal. Tendon reflexes were absent in the lower extremities. Bilateral ankle clonus was present but Babinski signs were absent. Chest x-ray and electrocardiogram were normal. The erythrocyte sedimentation rate (ESR) was 48mm/hr (Westergren); the venous hematocrit, 38%; and white blood cell count, 12,000/mm^3. Lumbar puncture revealed clear fluid and an opening pressure of 150mm. Cell count showed 53 red blood cells, and 198 leukocytes (44 neutrophils, 48 lymphocytes, and 8 monocytes) per mm^3; CSF glucose was 75mg/dl (blood glucose 120) and protein 122mg/dl. Gram stain, India ink preparations and subsequent bacterial, fungal and mycobacterial cultures of CSF were all negative.

The morning after admission, the patient showed diplegia and advancing muscle weakness in all extremities. Increasing respiratory difficulty ensued and the patient underwent nasotracheal intubation. Physical examination at that time revealed bilateral nystagmus on lateral gaze,

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decreased corneal reflexes and facial paralysis. Over the next two weeks, the patient had increasing respiratory difficulty and developed diffuse bilateral pulmonary infiltrates. A tracheostomy was performed and she was placed on antibiotic therapy and positive end expiratory pressure. Pneumothorax occurred and, despite intensive pulmonary support, the patient expired on November 5, 1977.

Virologic Investigation

The cerebrospinal fluid specimens collected on admission, October 22, and two days later, October 24, were inoculated individually into Rhesus monkey kidney (RMK), human embryonic kidney (HEK), and Hep-2 cell cultures. Throat and rectal swab specimens from October 24 were inoculated into RMK, HEK and into HeLa and WI-38 cell cultures. On October 27, repeat throat and nasal swabs were inoculated into RMK and HEK cells. The patient had developed herpetic-like lesions on her right thigh and vesicle fluid was collected and inoculated directly into HEK and HeLa cell cultures. A lung biopsy specimen taken at necropsy was macerated and inoculated into RMK and HEK cells.

Results

The presence of an enterovirus in the cell cultures (RMK, HEK, Hep-2) inoculated with the admission CSF specimens was suspected on November 3 by the appearance of characteristic cytopathic effects (CPE) consisting of rounding up of cells and toxicity of the cell culture. Neutralization tests in RMK cell cultures using a 10^{-1} dilution of the RMK passage virus as challenge dose showed a 50% reduction in CPE in the presence of pooled poliovirus antisera. Coxsackievirus A-9, B-1, B-2, B-3, B-4, and B-5, Echo-9, and poliovirus 2 and 3 antisera did not neutralize the viral isolate. Complete inhibition of CPE was noted with polio type 1 antiserum. Based on temperature sensitivity (New York City Department of Health) and polypeptide mapping (Dr. N. Young, NIH), the poliovirus 1 isolate was determined to be a “wild strain” as opposed to a “vaccine strain.”

Poliovirus was not recovered from the second spinal fluid (October 24) nor from throat, rectal and nasal swab specimens. Herpes simplex virus was isolated from nasal swab and vesicle fluid specimens. RMK cells inoculated with post mortem lung tissue hemadsorbed guinea pig red blood cells, indicating the presence of a myxovirus, subsequently identified as parainfluenzae type 2.

Antibody determinations performed with the admission and two day post admission sera revealed that the patient lacked humoral immunity to polio type 1 (<1:8) but had titers of 1:64 and 1:32 to polio types 2 and 3, respectively. The third serum showed a response to polio type 1 as evidenced by an increase in titer to >1:32 (Table 1). This serum neutralized the patient’s own isolate to a dilution of 1:4 as shown by inhibition of cytotoxicity in RMK.

Discussion

The last major outbreak of poliomyelitis in New York City was in 1949 when 2,446 cases and 179 deaths were recorded (1). In 1955, when the inactivated poliovirus (Salk) vaccine was introduced, there were 28,985 cases nationally (2) and 806 of these cases were in New York City (1). Starting with 1956, the number of reported cases declined sharply; in 1961, when the oral live poliovirus

TABLE I

Antibody Responses of Patient against Poliovirus

Date of Serum	Poliovirus/Reciprocal of Titer			
	type 1	type 2	type 3	CSF isolate
10/22/77	<8	>64	32	0
10/24/77	<8	>64	32	0
11/01/77	>32;<64	>64	64	4

(Sabin) vaccine was introduced, there were only two cases reported in New York City. From 1962 through 1972, only thirteen sporadic cases occurred in New York City (1).

The last major outbreak of poliomyelitis in the country occurred in 1972 in a Christian Scientist private school in Connecticut (3). Eleven cases of type 1 paralytic poliomyelitis occurred in a three-week period. None of the children had received polio vaccine because of their religious beliefs.

From 1973 through 1976, there were 30 domestic and 6 imported cases of poliomyelitis reported in the United States (4). All but three of the domestic cases were associated with the oral live poliovirus vaccine; eleven occurred in immunodeficient recipients. Of the remaining three cases, type 3 viruses were isolated from two cases and were classified as "vaccine-like" and "intermediate" with respect to their genetic markers; the other isolate was type 1 and was classified as "wild-type."

In addition to the case reported here, the Center for Disease Control recorded 16 cases of poliomyelitis in the United States in 1977 (5). Sixteen of these were domestic and two were imported. Four of the domestic cases occurred in Minnesota and were associated with four different lots of oral polio vaccine. Three of the domestic cases, including our case, had no history of receiving oral polio vaccine or of contact with a vaccine recipient. The source of infection in our case has not been identified. In addition to our fatal case, there has been one reported death in a vaccine-associated contact case (5).

The patient reported here had been vaccinated with inactivated poliovirus but nevertheless did not show protective antibody to poliovirus type 1. Epidemiologically, however, neither the number of doses administered nor the nature of the vaccine lots could be ascertained.

The apparent diminution in the level of postvaccination immunity has been of concern to public health authorities. In addition to the decreasing incidence of white and nonwhite children vaccinated against polio since 1965 (6), a 1975 serological survey conducted in a Michigan community revealed that postvaccination antibody titers were markedly diminished or absent (7). Oberhofer and colleagues assayed sera collected in 1966 and 1971 and showed that 20–30% of individuals aged 5–49 years lacked titers of at least 1:4 to one or more poliovirus types; with subjects 60 years and older the incidence increased to 60% (7). Using antibody levels of 1:16 or greater as an index of immunity, 30–50% of the population was considered susceptible to poliovirus types 1 and 2, and 40–60% to type 3 (7).

The duration of immunity produced by the polio vaccines is uncertain, and although the oral live poliovirus vaccine might be expected to induce a longerlasting immunity, the inactivated poliovirus vaccine has been shown to induce an antibody response detectable after a period of twelve years (4). Immunologic memory even in the absence of demonstrable antibody titers has been shown by a secondary-type response to booster injections seven to eight years after the last dose of inactivated poliovirus vaccine. The status of immunity of the population, especially among adults, in the United States in unknown and a serologic survey has been suggested by the Institute of Medicine Committee for the Study of Poliomyleitis Vaccines (6).

An unusual feature of this case was the isolation of type 1 poliovirus from the spinal fluid, a relatively rare occurrence. Poliovirus was isolated from spinal fluid in only three of 22 cases during an epidemic in 1959 (8). This is in contrast to other enteroviruses which are readily isolated from spinal fluid (9). The reason for this difference is not known.

The declining levels of immunity in the population may herald the occurrence of sporadic cases such as this or even local outbreaks. Physicians trained since the introduction of the poliovirus vaccines should be aware of this possibility and include poliomyelitis in the differential diagnosis of muscle weakness and paralysis.

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Health Effects of Low-Level Lead Exposure Among Iron Workers Repairing an Elevated Railway in New York City

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Abstract

Flame cutting of lead-painted steel structures may be associated with considerable lead exposure. The purpose of this study was to evaluate the health effects of lead exposure among iron workers repairing an elevated railway system in New York City, and to compare various biologic indicators of lead exposure between such workers and a control group. Zinc protoporphyrin (ZPP) determination as a diagnostic test for the medical surveillance of lead-exposed populations was also evaluated.

It was found that the iron workers had evidence of increased lead absorption as determined by ZPP, blood lead and hemoglobin levels. Twenty-one percent of the workers gave a history of lead-related symptoms even though their blood lead levels were within a commonly "acceptable" range. This study also demonstrated that zinc protoporphyrin is a more sensitive and accurate indicator of chronic lead exposure than is blood lead.

Introduction

Lead has been used since ancient times: its toxic effects were known to the Romans (1). Industrial growth during the past two centuries has led to an increasing demand for lead. It is estimated that 2.5 million tons of lead are processed yearly, 40% in the United States (2). Associated with increased demand, there is also a larger number of individuals at risk of undue industrial lead exposure. A United States Public Health Service publication of 1964 lists 113 potential types of occupational lead exposures (3), although improved occupational health supervision and efforts to minimize exposure to lead have greatly reduced the incidence of severe lead poisoning in lead trades since the early 1900s. Estimates of the magnitude of industrial health problems posed by exposure to lead are fragmentary, since adequate incidence data are not available (2).

Hazardous exposure to *organic* lead is limited to a relatively small number of workers employed in the manufacturing of tetraethyl and tetramethyl lead, although environmental exposure may be of importance.

Besides occupational groups there are also other people at risk of lead intoxication, albeit less frequently: producers of illegal whiskey ("moonshine")

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and those who drink beverages improperly stored in fireglazed pottery containing lead. The widespread use of old storagebattery casings as fuel (particularly during the Depression) has been another well-known source of poisoning.

In children, the extra milligrams of lead that cause poisoning are contained in the flakes of paint they may eat (pica) in dilapidated buildings. It should be noted that, in addition to the different natural histories of pediatric and adult plumbism, the routes of entry of lead compounds differ considerably in children and adults; in adults inhalation rather than ingestion poses the major problem. In young children of urban slums, lead poisoning is a major public health problem and may be associated with brain damage and behavioral problems (4). Lead has been found to be more toxic to the young (2), and intoxication may occur in the young at lower blood lead concentrations and often after relatively brief exposure (4). The available data suggest that 5–10% of preschool children residing in deteriorating urban housing consume sufficient lead to have "increased lead absorption" as measured by increased blood lead concentrations. Approximately one percent may be found to have symptoms compatible with clinical lead poisoning. The extent to which lead-bearing dust in ambient urban air may contribute to the problem is not known. As with occupational exposure, epidemiologic data concerning the incidence of lead poisoning in children is scanty. Housing in ghetto areas usually dates from the time when there were no restrictions on the use of lead in indoor paint. Current legislation prohibits the use of paint containing more than one percent lead solids by weight on interior surfaces. This restriction does not apply widely to *exterior* paint (which, therefore, may contain significant amounts of lead) that is used on both the inside and the outside of new wooden surfaces. Although the use of lead-containing paint has decreased in this country, red lead remains indispensible, especially as a weather-resistant coating for metals, and as a protective agent for ships, bridges, railings, and other iron and steel structures. Bridges and railings may be painted repeatedly in the course of maintenance, resulting in painted coatings that may attain thickness of an inch or more. While the use of metallic lead is rather safe, hazardous lead exposure commonly occurs when heat is applied to a lead surface, generating lead oxide fumes and dust. Welding, cutting, and grinding metal structures containing lead or covered with red lead paint have been widely recognized sources of lead poisoning since the 1920s, especially in connection with the dismantling of ships (5). Similarly, a recent study of ironworkers dismantling an elevated subway line in the Bronx, New York, demonstrated the potentially hazardous conditions with "burning" of metal; cases of overt lead poisoning were found (6). Further, a recent clinical survey of lead smelter workers demonstrated a high prevalence of adverse lead-induced health effects (7). The smelter workers, recovering lead from scrap storage batteries, were exposed to toxic lead fumes as the recovery process required heating of the metal.

In clarifying the currently used terminology connected with lead disease it is important to distinguish between "lead absorption" and "lead intoxication." The presence of excessive concentrations of lead in urine and blood indicates increased lead absorption but does not in itself express the actual biologic effect caused by the toxic metal. It is the adverse effect that is commonly associated with the term "lead intoxication."

The toxic effects of lead in man cover a broad spectrum. The main organ systems affected are the hematopoietic, nervous, gastrointestinal systems, and the kidneys. In the most severe forms of poisoning, profound disturbances of the central nervous system are prominent. Permanent brain damage may follow such acute events. Symptoms referable to the nervous system include headache, sleep disturbances, increased irritability, visual disturbances, convulsions, delirium, and coma. The most characteristic neurologic deficit is motor paralysis (wrist drop) that affects the most used muscle groups. This phenomenon may thus account for right-sided wrist drop in a right-handed individual with a simultaneously unaffected left wrist. Symptoms referable to the gastrointestinal system range from metallic or sweet taste, loss of appetite and weight loss, to nausea, abdominal discomfort, and lead colic—the latter being defined as crampy, abdominal pain associated with constipation lasting for several days.

Lead affects the hematopoietic system by inhibiting the biosynthesis of heme and the utilization of iron in red blood cells. Lead inhibits various enzymes in the synthesis of heme and the intermediate metabolites can be detected in the blood or urine (Fig. 1). "Asymptomatic" individuals with elevated blood lead concentrations (more than 40μg/100ml of whole blood) may be able to compensate by increasing their rate of red cell production (increase in reticulocytes) and, thereby, maintain a normal hemoglobin concentration. Continuous toxic stress however, may accentuate the impairment of heme biosynthesis. The hematopoietic tissue can no longer compensate by increased red cell production and failure of this compensatory mechanism is followed by anemia (2), usually hypochromic and normocytic in nature (2). In addition, erythrocyte life span may also be shortened in lead poisoning. Basophilic stippling of the red blood cells, possibly reflecting nuclear residues, is also a frequent finding.

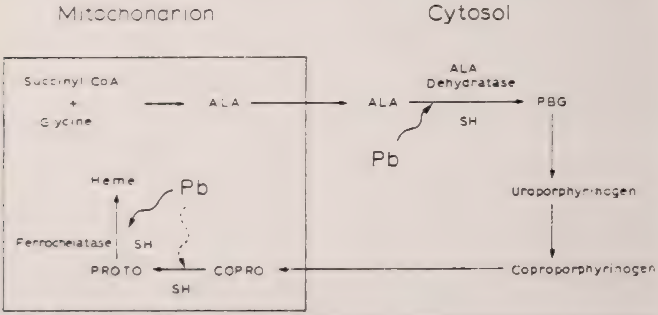

FIG. 1. Inhibition of heme biosynthesis by lead (Pb). Arrows indicate the site of enzymatic inhibition.

Although the interference with heme synthesis is a complex phenomenon, hematologic disturbances associated with lead poisoning are perhaps the most important part of the clinical picture of the disease, especially insofar as *early diagnosis* is concerned. Derangements in heme metabolism constitute the basis upon which various diagnostic tests have been developed. Thus, inhibition of delta-aminolevulinic acid dehydratase (ALA-D) has been shown to be a sensitive indicator of acute and chronic lead poisoning (8, 9). Similarly, large amounts of erythrocytic protoporphyrin, so called "free erythrocyte protoporphyrin" can be extracted from erythrocytes formed in lead burdened individuals (Fig. 1). Elaborate laboratory procedures limited the value and usefulness of this test for screening purposes. In 1974, however, Lamola and Yamane reported that erythrocytic protoporphyrin is not "free" but is chelated with zinc and is converted to zinc protoporphyrin (ZPP), detectable by fluorometry. Further development of fluorometric techniques has resulted in the design of a portable device, the *hematofluorometer* (10, 11, 12). This device uses a single drop of undiluted, unprocessed blood and provides a quantitative reading of the ZPP level in μg/100ml whole blood within a few seconds after the blood sample has been inserted into the apparatus.

It is important to distinguish between the different biologic connotations of blood lead and ZPP. These two indices for lead exposure depict different biologic phenomena. Blood lead concentration is an unstable parameter that reflects current or very recent lead absorption; it does not demonstrate a biologic effect. In contrast, ZPP reflects protoporphyrin elevation in the erythroid cells of the bone marrow as a result of the toxic effect of lead on heme biosynthesis. Protoporphyrin elevation is of necessity a delayed phenomenon (pari passu with red cell maturation and hemoglobin maturation) but is more persistent than the elevation in blood lead concentration (with the life of the red cell). A recent clinical field study by our Laboratory has shown ZPP determination to be highly useful in medical surveillance of lead-exposed workers (7).

There is ample evidence that chronic lead exposure may cause renal damage (13). The main structural changes are principally concentrated to the proximal convoluted tubules. A Fanconi syndrome (aminoaciduria, glycosuria, and phosphaturia) may develop. BUN and serum creatinine levels increase with duration of lead exposure, supporting an association between lead exposure and kidney function impairment (2).

The pathognomonic physical findings in lead-affected individuals are sparse; a gum "lead line" is occasionally found when poor oral hygiene is present. As mentioned, lead affects many organ systems of the body. The symptoms resulting from lead intoxication are nonspecific in nature and, unless there is an accompanying history of lead exposure, the diagnosis can be easily overlooked.

Recent studies (14) have indicated that currently "permissible" blood lead levels (80μg/100ml) in occupational circumstances may result in abnormalities in both the hematopoietic and nervous system, and that such blood levels should not be regarded as "safe."

There has been widespread challenge to the concept of lead poisoning as a "threshhold disease," i.e., that a certain blood lead level is needed in order to induce damage, and that below such a level no harmful effect would occur. The uncertainties concerning the threshold at which the effects of lead manifest themselves are reflected in the problem of long-term low-level exposure. The long-term consequences of sustained small increases in tissue lead content are incompletely known (2).

Present Study

We have investigated the health effects of lead exposure among a group of iron workers engaged in repair of an elevated railway system in New York City. Approximately half of the workers had been examined one year prior to the present study and some were at that time found to have lead induced hematologic abnormalities (15). In addition, we assessed the usefulness of zinc protoporphyrin (ZPP) determination (by the hematofluorometer) in the medical surveillance of this lead-exposed population, for the documentation of functional disturbances in the preclinical stage of lead disease. We also compared various biologic indicators of lead exposure among the lead exposed iron workers and in a control group of chemical workers.

Occupational Setting

The iron workers were members of the Iron Workers Local Union #40 and were repairing an elevated railway system built in the early 20th century. The use of oxy-acetylene-propane cutting torches was an essential feature in the work. The steel structure was covered with lead paint. As mentioned previously, hazardous lead exposure may occur when heat is applied to such surfaces, producing lead oxide and suboxide fumes and dust. The workers were observed at the worksite and examined in clinical facilities in the immediate vicinity of the worksite.

Methods of Investigation

A clinical field study of 34 iron workers in the New York City metropolitan area was conducted. All were volunteers and were interviewed with regard to their medical and occupational history. Each worker was also questioned concerning symptoms potentially related to lead effects and industrial hygiene procedures, including smoking and eating habits at the worksite, using specially designed questionnaires of the Environmental Sciences Laboratory. These had been used and validated in previous studies (7). All underwent a comprehensive physical examination with special attention to signs possibly related to lead toxicity.

A control group of forty-one workers employed at a chemical factory in New Jersey was studied. Members of the Oil, Chemical and Atomic Workers Union were invited to participate in a clinical field examination in a Paterson New Jersey Clinic, used by Mount Sinai as a field station. These workers were also interviewed regarding their medical and occupational history. However, they were not specifically interviewed with regard to symptoms potentially related to lead effects. Chemical workers with a positive history of lead exposure were excluded from this study (7 workers), leaving a total of thirty-four chemical workers as controls. This group of workers also underwent a comprehensive physical examination.

All workers (both the study group and controls) had venous blood samples drawn at the field site. A broad spectrum of laboratory tests were performed by the Department of Chemistry of The Mount Sinai Hospital. All thirty-four iron workers had blood lead determination done while twenty-three randomly selected chemical workers had this test performed. Blood lead was determined by atomic absorption spectrophotometry. The iron workers had peripheral blood smears done to seek basophilic stippling; serum iron and iron binding capacity were also determined. Complete blood counts hemoglobin, hematocrit, red blood cell indices, total white blood cell count and clinical biochemistry studies were done in both groups. The effect of lead on hemesynthesis system was investigated by zinc protoporphyrin (ZPP) determinations (ZPP-meter, Aviv Associates, Lakewood, New Jersey 08701) in both groups of workers.

Results

Thirty-four male iron workers were examined. Twenty-five (74%) were white and nine (26%) black. The age distribution is shown in Table I. The mean age was 41.3 years (± 11.2 yrs.). The mean duration of employment, illustrated in Table III was 15.1 yrs. (± 11.2 yrs.). Ten workers (29.4%) were exposed for less than five years while 11 workers (32.4%) had more than 21 years of experience as iron workers. The present duration of work at the elevated railway, is displayed in Table IIIA. The mean duration of employment was 12.2 months (± 3.8 months) and only five workers (15%) had been employed for six months or less.

The control group of 34 chemical workers were all white males. The age distribution of these workers is shown in Table II. The mean age was 41.4 years (± 14.6 years) and their mean duration of employment, illustrated in Table IV, was 13.5 years (± 12.9 years).

TABLE I

Age Distribution of 34 Iron Workers Employed at Elevated Railway

Age (years)	Number	Percent
<30	6	17.6
30–39	12	35.3
40–49	8	23.5
50+	8	23.5
Total	34	100.0

TABLE II

Age Distribution of 34 Chemical Workers

Age (years)	Number	Percent
<30	12	35.2
30–39	4	11.8
40–49	4	11.8
50+	14	41.2
Total	34	100.0

TABLE III

Duration of Employment as Iron Workers

Time (years)	Number	Percent
≤5	10	29.4
6–10	5	14.7
11–15	3	8.8
16–20	5	14.7
21+	11	32.4
Total	34	100.0

TABLE IIIa

Duration of Employment of Iron Workers at Elevated Railway

Time (months)	Number	Percent
3–6	5	14.7
7–12	10	29.4
13–18	19	55.9
Total	34	100.0

TABLE IV

Duration of Employment of Chemical Workers

Time (years)	Number	Percent
≤5	14	41.2
6–10	5	14.7
11–15	2	5.9
16–20	2	5.9
21+	11	32.3
Total	34	100.0

Symptoms

The first group of symptoms explored among the iron workers were *central nervous system (CNS) symptoms* including dizziness, headache, weakness, hyperirritability, nervousness, and sleep disturbances; none reported such symptoms. With regard to *gastrointestinal symptoms*, including metallic or sweet taste, loss of appetite and weight loss and lead colic, one worker (grinder) reported a history of loss of appetite and weight loss. Upon further investigation it was discovered that this individual worked in the immediate vicinity of a burner and that he did not wear a respirator. His ZPP level was 84μg/100ml and his blood lead level 56μg/100ml. Six other workers (18%), four of whom "burned" regularly and two who did occasional burning, reported having a metallic or sweet taste. Only one of these individuals wore a respirator regularly. The mean ZPP of these six workers was 57.5μg/100ml (range 36–90μg/100ml and their mean blood lead level was 41.8μg/100ml (range 26–58). There were no reported complaints of nausea, abdominal discomfort or lead colic. Physical examination of both groups of workers (chemical and iron workers) did not reveal any tremor, muscle weakness or lead line.

Zinc protoporphyrin

The mean ZPP of the iron workers (Table V) was 57.4μg/100ml (±32.8). The ZPP value ranged from 20–190μg/100ml. The workers were divided into three job categories: "frequent" burners, 41% (14 workers), "occasional" burners, 38% (13 workers), and nonburners 21% (7 workers). The frequent burners had a mean ZPP of 60.5μg/100ml and mean blood lead of 40μg/100ml, while the occasional burners had mean values of 63.2μg/ml and 41.4μg/100ml respectively. The workers who did not burn had a mean ZPP of 40.4μg/100ml and blood lead of 37.9μg/100ml. Twenty-eight percent of the frequent burners, and 7.7% of the occasional burners wore respirators regularly. Comparison of the mean blood lead and ZPP levels between the three job categories was done (independent sample t-test). A significant difference between the mean ZPP values was found between frequent burners and workers who did no burning ($p = .07$). Due to the small sample size, this p value is considered to denote significance. However, there was no significant difference in the blood lead levels between these two groups. The workers who occasionally burned were

TABLE V

Zinc Protoporphyrin Levels of 34 Iron Workers

Zinc protoporphyrin μg/100 ml	Number	Percent
<50	17	50.0
50–79	8	23.5
80–99	8	23.5
100+	1	3.0
Total	34	100.0

also compared to the group who did no burning at all with regard to mean ZPP and blood lead levels: no significant difference was found for either parameter.

The distribution of ZPP values in the chemical workers is shown in Table VI. The mean ZPP for the group was 39.5μg/100ml (± 6.5) with a range of 29 to 53μg/100ml. The mean ZPP values of iron and chemical workers were found to be significantly different ($p < .01$).

Blood lead

The blood lead levels of the iron workers are shown in Table IX. The mean blood lead concentration was 40.1μg/100ml (± 13.1). None of the blood lead values exceeded the current Occupational Safety and Health Administration recommendation of 80μg/100ml. The blood lead levels of the chemical workers is shown in Table X. The mean value was 22.8μg/100ml (± 6.9). A significant difference was found between the two groups of workers ($p < .001$).

Hemoglobin

The distribution of hemoglobin values of the iron workers is shown in Table VII. The mean hemoglobin level was 15.2gm/100ml (± 0.89) with a range of 12.9 to 17.6gm/100ml. The three workers with low hemoglobin values (below 14gm/100ml) had ZPP values between 60–80μg/100ml and blood lead levels between 32–50μg/100ml. Their duration of employment at the railway worksite ranged from 12 to 14 months; they had 7 to 25 years' employment as iron workers. The hemoglobin levels of the chemical workers is displayed in Table

TABLE VI

Zinc Protoporphyrin Level of 34 Chemical Workers

Zinc protoporphyrin μg/100ml	Number	Percent
<50	31	91.2
50–79	3	8.8
80–99	0	—
100+	0	—
Total	34	100.0

TABLE VII

Hemoglobin Levels of 34 Iron Workers

Hemoglobin (gm/100ml)	Number	Percent
12.0–14.0	3	8.8
14.1–15.0	12	35.3
15.1–16.0	14	41.2
16.1–18.0	5	14.7
Total	34	100.0

TABLE VIII

Hemoglobin Levels of 34 Chemical Workers

Hemoglobin (gm/100ml)	Number	Percent
12.0–14.0	2	5.9
14.1–15.0	5	14.7
15.1–16.0	13	38.2
16.1–18.0	14	41.2
Total	34	100.0

TABLE IX

Blood Lead Levels of 34 Iron Workers

μg/100ml	Number	Percent
≤19	2	5.9
20–39	16	47.0
40–59	14	41.2
60–79	2	5.9
80+	0	0.0
Total	34	100.0

TABLE X

Blood Lead Levels of 23 Chemical Workers

μg/100ml	Number	Percent
≤19	7	30.4
20–39	16	69.6
40–59	0	0.0
60–79	0	0.0
80+	0	0.0
Total	23	100.0

VIII; the mean hemoglobin value was 15.8 (± 0.89) and the values ranged from 13.8 to 17.2. Two workers with hemoglobin values below 14gm/100ml had ZPP values of 31 and 39μg/100ml. The mean hemoglobin concentrations were significantly different between the two groups of workers ($p < .01$).

Comparison with previous survey

Nineteen of the thirty-four iron workers had been examined approximately one year prior to the present survey. Their ZPP levels are displayed in Tables XI and XII. The mean ZPP level of these workers had been 63μg/100ml (± 59.4), while the mean value for the same individuals was 54.5μg/100ml (± 39.6) in the current study. The mean ZPP values were not found to be significantly different. The mean blood lead levels were also examined (Tables XIII, XIV); and a mean blood lead concentration of 28.3μg/100ml (± 11.6) was found during the previous examination while the current mean value was 39.8μg/100ml (± 14.4); there was a statistically significant difference at the $p < .01$ level.

TABLE XI

Zinc Protoporphyrin Levels of 19 Iron Workers Examined October 1976

Zinc protoporphyrin µg/100ml	Number	Percent
<50	12	63.2
50–79	2	10.5
80–99	1	5.3
100+	4	21.0
Total	19	100.0

TABLE XII

Follow-up Zinc Protoporphyrin Levels of 19 Iron Workers Examined October 1976 and December 1977

Zinc protoporphyrin µg/100ml	Number	Percent
<50	9	47.4
50–79	5	26.3
80–99	4	21.0
100+	1	5.3
Total	19	100.0

TABLE XIII

Blood Lead Levels of 19 Iron Workers Examined October 1976

Blood lead µg/100ml	Number	Percent
<19	5	26.3
20–39	11	57.9
40–59	3	15.8
60–79	0	0.0
80+	0	0.0
Total	19	100.0

TABLE XIV

Follow-up Blood Lead Levels of 19 Iron Workers Examined October 1976 and December 1977

Blood lead µg/100ml	Number	Percent
≤19	2	10.5
20–39	8	42.1
40–59	7	36.9
60–79	2	10.5
80+	0	0.0
Total	19	100.0

Correlative Studies

For both chemical and iron workers ZPP and blood lead levels were analyzed using the Pearson correlation coefficient with regard to independent variables of total duration of employment hemoglobin level, and present employment (iron workers). For iron workers, the ZPP was significantly correlated with total duration of employment ($r = .40$, $p < .01$). The hemoglobin level showed a significantly negative correlation with present employment at the railway, ($r = -.30$, $p < .05$). Blood lead levels were found to have no significant correlation with any of the above independent variables. There were no significant correlations among the same parameters for the chemical workers. When blood lead was correlated with ZPP for each group of workers, a significant correlation was found ($r = .66$, $p < .01$) among the iron workers; however, there was no significant correlation found among the chemical workers.

Serum iron, iron binding capacity, and clinical chemistry

Serum iron and iron binding capacity were also studied. All values were within normal limits excluding iron deficiency as a source of elevated ZPP levels. All SMA-12 measurements in both groups were within normal limits. The following 16 biochemical constituents of blood were measured on Sequential Multiple Analyzer with Computer: glucose, urea nitrogen, creatinine, sodium, potassium, chloride, uric acid, calcium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, SGOT, SGPT and CPK. The results in both groups were within normal reference limits.

Discussion

In this clinical survey, two different populations of workers were studied: iron workers with potentially hazardous lead exposure and chemical workers not exposed to lead. The age distribution of both groups of workers were similar as was duration of employment.

Few reported lead-related symptoms were found among the iron workers and physical examination was essentially negative in both groups. The paucity of lead-related symptoms among the iron workers is not surprising since their mean ZPP and blood lead levels were 57.4μg/100ml and 40.1μg/100ml respectively. In a recent study of cable splicers by Fischbein et al (16), eleven percent reported gastrointestinal symptoms among individuals with ZPP levels below 50μg/100ml. This increased to forty percent when ZPP levels exceeded 80μg/100ml. Although the blood lead levels of the iron workers were within acceptable range, 21% of the workers reported mild lead-related gastrointestinal symptoms. In a study of smelter workers by Lilis et al (7) nineteen percent of the workers with blood lead levels less than 60μg/100ml reported more significant gastrointestinal symptoms.

The mean ZPP values of the iron and chemical workers (57.4μg/100ml and 36.6μg/100ml) were found to be significantly different ($p < .01$). The mean blood lead levels for each group were also compared (40.4μg/100ml, 22.8μg/100ml) revealing a significant difference ($p < .001$). Thus the group of iron workers was significantly different from the chemical workers studied, with respect to ZPP and blood lead values. Lead absorption among the iron workers manifested itself in relatively few overt clinical symptoms, however, cumulative absorption was reflected in abnormalities in the hematopoietic system.

The iron workers were grouped into three occupational categories: those with frequent burning (14 workers or 41%), occasional burning (13 workers or 38%) and those with no burning at all (7 workers, 21%). It was observed that only 28% of the frequent burners and 7.7% of the occasional burners actually used respirators. When the mean blood lead and ZPP levels of the three job categories were analyzed, a statistically significant difference was found between the mean ZPP values ($p = .07$) of the workers who burn frequently and those who do no burning at all. However, there was no significant difference between the mean blood lead concentrations of these two groups of workers.

The mean hemoglobin values were 15.1 and 15.8gm/100ml for the iron workers and the chemical workers respectively. The values were found to be significantly different ($p < .01$). Three iron workers with low hemoglobin values had elevated ZPP levels. Two chemical workers with hemoglobin values below 14gm/100ml had normal ZPP values (31 and 39μg/100ml) suggesting that these two cases of anemia in the control group were not lead related.

In both the iron and chemical workers ZPP levels and blood level values were analyzed with regard to independent variables: total duration of employment, hemoglobin level and duration of present employment (only iron workers). The iron workers' ZPP levels were significantly correlated with total duration of employment ($r = .40$, $p < .01$). In addition, the iron workers' hemoglobin levels obtained a significant negative correlation with present employment at the railway ($r = -.30$. $p < .05$). The blood lead levels did not show any significant correlation with any of the above mentioned independent variables for either group.

Analysis of the association between blood lead and ZPP by group, revealed a significant correlation ($r = .66$, $p < .01$) among the iron workers, while no significant correlation was found among the group of chemical workers. A curvilinear relationship between blood lead and ZPP was expected due to the different kinetics of these two parameters. The blood lead level represents only a small fraction of the total body burden of lead and constitutes a valid indicator for recent or current lead absorption. Zinc protoporphyrin, however, reflects the biologic response to the effect of lead on the bone marrow and has been shown to be present in erythrocytes during the lifetime of the cell (120 days). Thus, ZPP reflects an integrated long-term effect. It was of interest to note that the variation in ZPP over a one year period was very small in 19 ironworkers. However, there was a significant difference ($p < .01$) between their mean blood lead concentration over one year's observation. These workers experienced continuous relatively low lead exposure.

ZPP and blood lead levels of the iron workers were analyzed with respect to various other biochemical and environmental parameters. The intragroup comparisons performed were between workers with basophilic stippling of their red blood cells versus workers without basophilic stippling; between workers who eat at the work site and workers who do not eat at the work site; between smokers versus nonsmokers; and between workers with sweet or metallic taste versus workers without such symptoms. In all the above comparisons, no significant differences were found between mean values of both ZPP and blood lead. This finding further indicates that environmental factors such as smoking and consumption of food at the work site did not contribute significantly to the magnitude of increased lead absorption, but that this might be attributed to the occupational exposure alone.

Summary

Iron workers using oxy-acetylene propane cutting torches in the repair of an elevated railway may experience significant lead exposure. The relatively low level of exposure did not result in overt clinical lead poisoning.

ZPP is a more sensitive and accurate indicator of chronic lead exposure than is the blood lead level.

Few workers had lead-associated symptoms but nevertheless demonstrated changes in the hematopoietic system, reflected by elevated ZPP levels and decreased hemoglobin concentrations.

Medical evaluation of the presence or absence of lead-induced biologic effects should include, in addition to clinical examination, laboratory parameters denoting absorption (blood lead) as well as biologic responses (ZPP and hemoglobin). Adherence to such principles will assist in proper medical surveillance of populations at risk of undue lead exposure.

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Renal Artery Injury following Blunt Abdominal Trauma

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Abstract

This is a case report of intimal tear of the left renal artery caused by a fall. Contrary to the majority of cases of this type reported, this patient did not develop renal artery thrombosis. Renal function was restored by resection of the damaged segment and anastomosis.

Introduction

Although renal artery thrombosis following blunt abdominal trauma is being recognized more frequently, the renal salvage rate remains distressingly low. Until 1975, over 40 cases had been reported in the literature (1) but only four had documented preservation of some renal function (2–5). The majority of patients developed recurrent thrombosis and persistent hypertension, requiring nephrectomy (6–10). All of these are caused by acceleration-deceleration injuries producing intimal tears near the origin of the renal artery with subsequent subintimal dissection and thrombosis. The left renal artery is affected more often than the right and occasionally, patients with bilateral thromboses have been reported (2, 4, 7, 11). This is a case report of intimal tear of the left renal artery producing compromise in renal function but without thrombosis.

Case Report

A 26 year old male was admitted to the Mount Sinai Services—City Hospital Center at Elmhurst following a fall from a third story window, in clinical shock. The patient was alert, oriented, pale, and unable to move the lower extremities. Blood pressure was 90 mmHg. by palpation and the pulse 120 per minute. The abdomen was rigid and diffusely tender. X-rays revealed a fracture of the tenth thoracic vertebra and on physical examination there was complete transection of the spinal cord at this level. There were associated fractures of the body of the second lumbar vertebra, the transverse processes on the right side from T-12 to L-5 and the right twelfth rib. Hematocrit on admission was 43%. Urinalysis revealed 10–15 red blood cells per high power field. The intravenous pyelogram showed prompt excretion of the dye on the right side with lateral displacement of the kidney and obliteration of the psoas margin. On the left side, only a nephrogram phase was seen after 30 minutes but no excretion of the dye. Cystogram was normal. The patient remained hypotensive and was taken to the operating room following immediate resuscitation.

At laparatomy, a retroperitoneal hematoma was found on the right side without active bleeding. Examination of both kidneys showed no gross evidence of trauma and appeared unremarkable. The renal artery was not explored. Angiography performed after surgery revealed an intimal tear of the left renal artery, 2 centimeters from its origin, without thrombosis of the vessel (Fig. 1). Approximately 20 hours from the time of injury, the patient was reexplored. The intimal tear was

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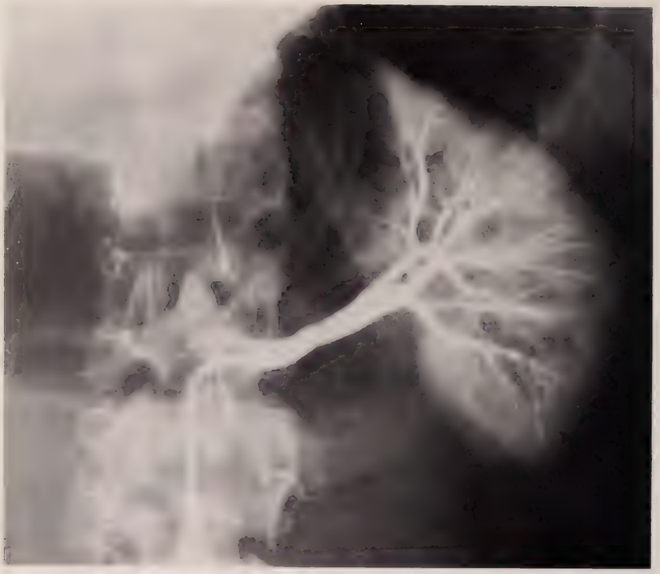

FIG. 1. Shows intimal tear of the left renal artery 2 centimeters from its origin.

confirmed and there was subintimal dissection and aneurysmal dilatation for a distance of about 1 centimeter. There were no palpable pulsations distal to the area of injury but there was no thrombosis. The damaged area was resected and an end-to-end anastomosis was performed. Following that, pulsation was felt throughout the length of the artery. The left renal vein was normal. Patency of the anastomosis was confirmed by angiography one week later (Fig. 2).

The postoperative course was uneventful except for moderate hypertension after the renal revascularization procedure. This lasted four days and then the blood pressure returned to normal. Intravenous pyelogram performed two weeks later revealed a functioning left kidney with delayed excretion of the dye. The patient remained normotensive and was subsequently discharged to another hospital where he is being treated for his paraplegia.

Discussion

Renal artery damage following blunt abdominal trauma probably occurs more frequently than presently recognized. All the cases reported showed thrombosis due to intimal tears near the origin of the renal artery. There is only one case, to our knowledge, similar to ours reported by Bryniak and Morales in which the intimal tear was not associated with thrombosis (12). There are, however, several reports of renal artery stenosis with hypertension following abdominal trauma (13, 14). These represent cases where the initial diagnosis was missed and they were readmitted several months later with

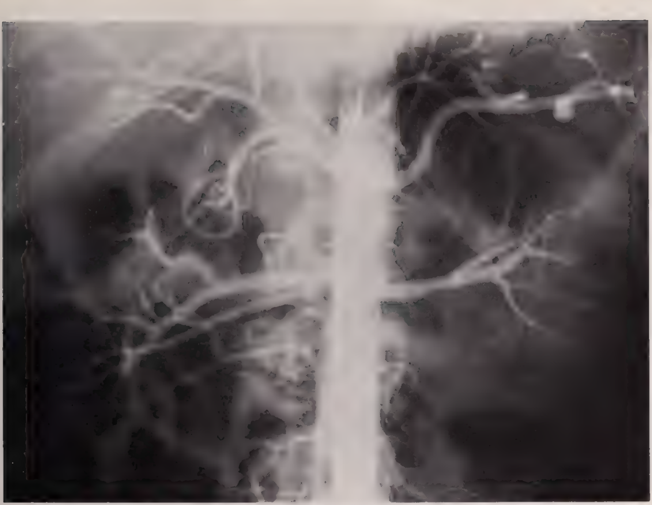

FIG. 2. Arteriogram one week after resection of injured segment of the left renal artery. The anastomosis is patent.

severe hypertension. These patients were found to have organized thrombi in the renal artery at the site of stenosis. Revascularization or nephrectomy resulted in return of the blood pressure to normal.

All patients with blunt abdominal trauma accompanied by hematuria should have an intravenous pyelogram at the time of admission. If there is delayed excretion of the dye on one side, selective renal angiography should be performed to rule out injuries to the renal artery. If intimal tear is present, even without thrombosis, renal artery exploration and repair is indicated to prevent development of renal artery stenosis or thrombosis and subsequent hypertension. Nonoperative treatment (12) should probably be reserved for the critically ill in whom major surgical intervention is not warranted.

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Combined Perineuritis and Vasculitis Associated with Uterine Prolapse: A Report of Two Cases

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EVALYNNE V. BRAUN, M.D.

Abstract

The uterine cervix of two women who had uterine prolapse revealed interstitial neuropathy, necrotizing vasculitis and perivasculitis. The patients did not show neurologic symptoms. It is speculated that the lesions are secondary to the pressure exerted by the pessary, with subsequent nerve injury and chronic inflammation.

Over the past year we have encountered an entity characterized by isolated inflammation around, and occasionally involving, the peripheral nerve bundles of the uterine cervix. The patients showed no neurologic symptoms. The standard textbooks in gynecology (5, 7) and gynecologic and surgical pathology (1, 4) do not mention this entity and, to our knowledge, it has not been reported previously. The present communication describes the morphology and clinical associations of this uncommon condition.

Case Reports

Case 1. A 57-year-old gravida VI, para VI white woman was admitted to the hospital because of symptomatic prolapse that had been treated for many years by a "doughnut" pessary. The ages of her children ranged from 17 to 31. She became menopausal at age 50. Physical examination was essentially normal. The laboratory data were unremarkable. Physical examination showed a large cystocele with second degree uterine prolapse. The clinical impressions were pelvic relaxation, cystocele and uterine prolapse. The patient underwent vaginal hysterectomy, anterior colporrhaphy and posterior colpoperineorrhaphy.

Pathology: Grossly, the specimen consisted of uterus without adenxa weighing 45 grams and measuring 7.5 × 4.8 × 3 cm. The uterine cervix was enlarged and measured 2.5 cm in maximum dimension. The myometrium measured 1.5 cm in maximum thickness. The endometrium was smooth and slightly hemorrhagic. A small endocervical polyp measuring 0.4 cm was present. Multiple fragments of vaginal mucosa were also submitted.

Microscopically, there was nonspecific chronic cervicitis, atrophic endometrium, and a benign endocervical polyp. The stroma of the cervix contained hypertrophied nerve bundles, most of which were surrounded by a thick collar of mononuclear cells, predominantly lymphocytes (Fig. 1). The nerves that were present in the pericervical fibroconnective tissue showed a similar change. In addition, the ganglia showed both a chronic perineuritis and endoneuritis (Fig. 2). Although most blood vessels were unremarkable, a few large arteries showed focal necrosis, vasculitis (Fig. 3), and occasionally, perivasculitis (Fig. 4). The cervical stroma was devoid of significant inflammatory infiltrate. The body of the uterus did not show significant pathologic changes.

The postoperative course was uneventful and the patient is well six months after surgery.

Case 2. A 63-year-old woman with a history of myasthenia gravis for 25 years was admitted for surgical repair of uterine prolapse. Three years previously the uterine prolapse was diagnosed and she was treated with a pessary. Prior to admission, the use of the pessary was intermittently

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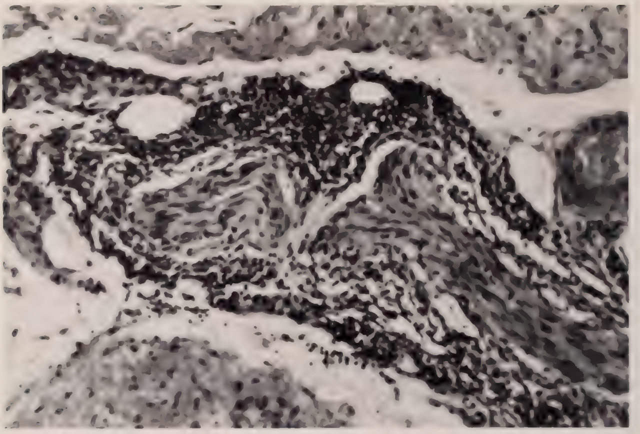

FIG. 1. Longitudinal section of nerve bundle showing intense perineural lymphocytic infiltration. The nerve fibers do not show degeneration. Note the surrounding cervical stroma is devoid of chronic inflammation (H & E, × 100).

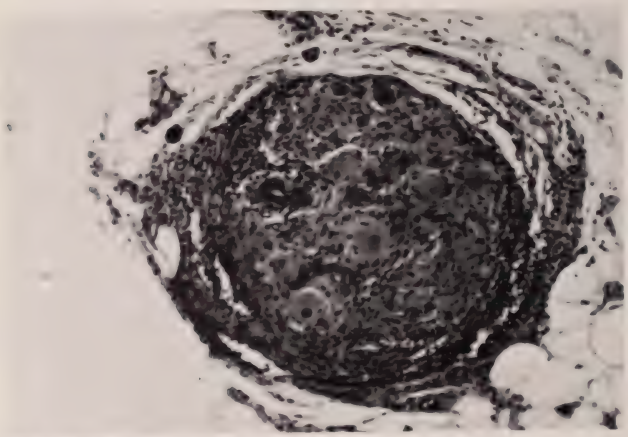

FIG. 2. Photomicrograph of section through a ganglion in pericervical connective tissue showing peri- and endoneuritis (H & E, × 100).

discontinued because of vaginal ulceration. The pessary had failed to control her stress incontinence. Physical examination revealed third degree uterine prolapse with marked redundancy and eversion of the vaginal wall. She underwent dilation and curettage, amputation of cervix, anterior and posterior colporrhaphy and perineorrhaphy.

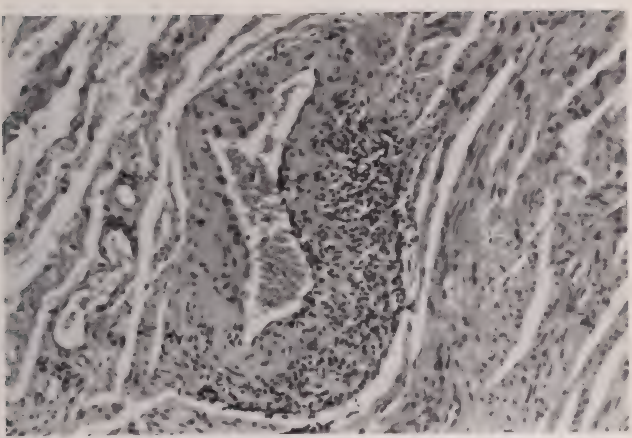

FIG. 3. Section of artery showing focal necrosis and chronic inflammatory infiltrate. The surrounding stroma lacks significant chronic inflammation (H & E, × 100).

Pathology: The uterine cervix, which measured 3.2 × 4.5 × 2.5 cm was hypertrophied and showed an enlarged external os measuring 2.8 cm in maximum dimension.

Microscopically, the uterine cervix showed keratinized and hyperkeratotic mucosa and nonspecific chronic inflammation. The changes occurring in the nerves and blood vessels of the stroma and pericervical connective tissue, though of less severity, were similar to those described in Case 1. The postoperative course was uneventful and the patient continues to take prostigmine for myasthenia gravis.

Discussion

Peripheral neuropathy has been morphologically classified as parenchymatous, interstitial, or vascular (3). The parenchymatous type is characterized by primary involvement of the neuronal cell body or the myelin sheath by wallerian degeneration or segmental demyelination. By contrast, the initial lesion in interstitial neuropathy lies in the interstitial connective tissue and vascular spaces of the nerve; wallerian degeneration may occur secondarily. In vascular neuropathy, the lesion, primarily situated in the blood vessels, may be inflammatory, atheromatous or mechanical, leads to ischemia of the nerve with subsequent infarction and wallerian degeneration. Important etiologic considerations in peripheral neuropathy include inflammatory, metabolic, neoplastic, mechanical and degenerative diseases and following chemotherapy. Constant and prolonged pressure upon the peripheral nerve can lead to structural and functional changes (2).

Nonspecific inflammatory changes in the spinal ganglia and peripheral nerves have been reported in approximately 5% of routine autopsies. These abnormalities are characterized by cellular infiltrate, predominantly lymphocytes, and occasional degenerative changes in the axons and the myelin sheath.

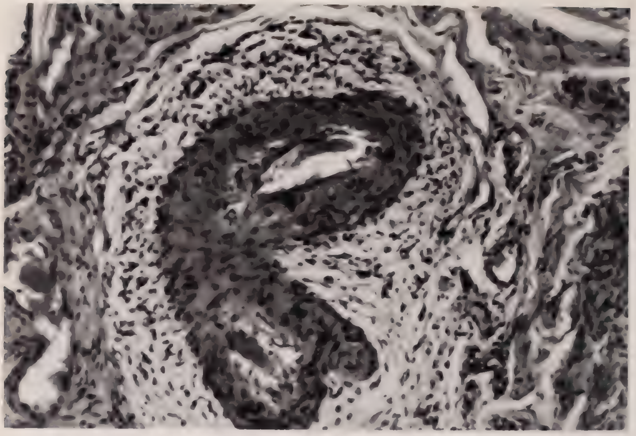

FIG. 4. Artery showing intact wall but moderate perivascular inflammation and fibrosis (H & E, × 100).

The patients are symptomless and the lesions are more related to the state of the body rather than a primary disease of the nervous system. The inflammatory involvement of the nerves in the uterine cervix in the two patients reported here may be classified as the interstitial type of mononeuritis. A survey of 200 uteri removed for various causes revealed 30 prolapsed uteri of which 19 were treated with different types of pessaries. None of these uteri showed neuritis or perivasculitis corroborating the infrequent occurrence of this type of lesion. Notwithstanding, we relate the pathogenesis of the lesion to the pressure caused by the pessary with subsequent chronic inflammation. The unusual features of these cases lie in the almost exclusive involvement of the nerves and ganglia, scattered vasculitis and perivasculitis and the absence of significant inflammation of the cervical stroma.

Recently Pirozynsky reported two cases of giant cell arteritis of the uterus that was found incidentally in association with uterine prolapse (6). Although no convincing explanation was given for the occurrence of the arteritis, the author attempted to relate the uterine findings with temporal arteritis and polymyalgia rheumatica. Our patients showed both neuritis and necrotizing arteritis and periarteritis. The fact that the patients were asymptomatic would indicate that the presence of these changes in the uteri of women with prolapse is incidental and probably of no functional significance.

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Cefamandole: A New Cephalosporin for Therapy of Hospitalized Patients with Infection

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PETER NICHOLAS, M.D., AND SHALOM Z. HIRSCHMAN, M.D.

Introduction

Cefamandole is a new cephalosporin derivative with a broad spectrum of antimicrobial activity against a variety of gram-positive and gram-negative bacteria (1–3). Studies in vitro have shown cefamandole to be extremely active against strains of Hemophilus influenzae (1–3). The drug is also active against a significant number of Escherichia coli, Klebsiella pneumoniae, and indole-positive Proteus resistant to other cephalosporins (4). Cefamandole can be administered either intravenously or intramuscularly and pharmacokinetic studies have shown that very high drug levels are achieved in serum following administration by either route (5). We have conducted a study of the clinical efficacy of cefamandole in the treatment of a variety of infections in hospitalized, seriously ill patients and now report the results of this investigation.

Materials and Methods

The patients were all hospitalized either at The Mount Sinai Hospital, New York or the Elmhurst General Hospital, Elmhurst, New York. All patients included in the study had clinical evidence of infection. Patients with bacteremia had fever, chills or hypotension. Patients with pneumonia had chest x-ray evidence of infiltration, in addition to leukocytes and bacteria in sputum obtained either by transtrachial aspiration, fiberoptic bronchoscopy, or two or more expectorated specimens. Patients with osteomyelitis had radiologic evidence of bone destruction and a pathogen was isolated from drainage or by direct aspiration of the lesion. Patients with urinary tract infections had fever, dysuria, frequency, urgency and pus cells in urine.

Cefamandole was administered intramuscularly in doses ranging from 4 to 12 gm/day given every six or four hours. Intravenous administration of cefamandole was through a Soluset diluted in 50cc, administered over a 15 minute period in doses of 1–2 gm every 4–6 hours. Informed consent was obtained from each patient according to institutional policy.

Cultures were taken from appropriate sites prior to therapy and were processed by the diagnostic microbiology laboratories of The Mount Sinai and Elmhurst General Hospitals. The minimum inhibitory (MIC) and minimum

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bactericidal concentrations (MBC) of cefamandole for the isolate was determined by the broth dilution method as previously described (3). Susceptibility of cefamandole by disc diffusion test was also determined using a 30 μg disc by the method of Bauer et al (6). Cefamandole serum levels were measured by the disc diffusion method using Bacillus subtilis as the test organism as previously described.

Laboratory studies performed before, during and after therapy included hemogram, serum urea nitrogen, creatinine, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), alkaline phosphatase, bilirubin, calcium, uric acid, phosphorous, albumin and globulin, and urinalysis. Patients were also observed for possible side effects to the drug including examination of skin for rash.

Patients were considered improved if they became afebrile and other signs of infection abated. Patients were considered cured if they became afebrile, signs of infection disappeared, and cultures became negative. Patients were classified as having failed on cefamandole therapy if infection did not clear clinically and the pathogen was not eradicated.

Results

Forty-three hospitalized patients were treated with cefamandole during the study period of 7/1/76–6/30/77. Of these patients, five are not included in the evaluation because of failure to prove infection. Thus, 38 patients with infection were treated and ranged in age from 20 to 82 years (Table I). There were 23 females with a mean age of 48.4 years and 20 males with a mean age of 49.4 years (Table I). The most frequent infection was pneumonia with 16 patients, followed by bacteremia in 15 patients, 12 patients with soft tissue infection and 5 patients with urinary tract infection for a total of 48 infections in the 43 patients.

Most of the patients had underlying diseases. The most common of these were cardiovascular and pulmonary diseases (Table II). The other underlying diseases included neoplasia, drug addiction, alcoholism, myeloproliferative disorders, renal disease and diabetes mellitus.

Thirty-two organisms were isolated from the patients, including 16 gram-positive and 16 gram-negative isolates (Table III). All the isolates were susceptible to concentrations of 12.5 μg of cefamandole. The gram-negative isolates included 3 of Hemophilus influenzae (Table III).

Cefamandole was given either intravenously or intramuscularly for 2 to 42 days. Seventy-four percent of patients received the drug for more than 7 days. The total dose ranged from 8 to 504 gm. Serum levels of cefamandole one hour following a 1 gm dose intravenously ranged between 13.8 to 54 μg/ml with a mean level of 27.16 μg/ml. The average serum level of cefamandole one hour following 2 gm doses given intravenously was 36 μg/ml.

Bacteremias

There were 15 patients with bacteremia, including 6 patients with endocarditis, 4 patients with soft tissue infections, 2 patients with urinary tract

TABLE I

Sex and Age Distribution of Patients Treated with Cefamandole

Infection	Sex	No. of Patients*	Mean Age (yrs.) (range)
Bacteremia	M	9	44.7 (24–82)
	F	6	62.2 (50–73)
Soft Tissue	M	5	38 (23–73)
	F	7	44.6 (20–73)
Pneumonia	M	7	57.1 (23–80)
	F	9	43 (22–70)
Urinary tract	M	1	82
	F	4	59.5 (46–77)
Total patients treated	M	20	49.4 (23–82)
	F	23	48.4 (20–77)

* Three patients with soft tissue infection and two with urinary infection also had bacteremia and are included in both categories.

TABLE II

Underlying Major Diseases of Patients Treated with Cefamandole

Disease	Number of Patients
Cardiovascular	9
Pulmonary	7
Neoplasia	6
Drug Addiction	4
Alcoholism	5
Myeloproliferative disorder	4
Renal	3
Diabetes mellitus	3

infection and 1 patient with typhoid fever and another with empyema. The bacterial isolates from the patients with endocarditis included 3 of Staphylococcus epidermidis, 2 of S. aureus and one Eikenella corrodens. The isolates from the other patients with bacteremia included Escherichia coli (2), Proteus mirabilis (2), α-hemolytic streptococcus (1), Salmonella typhi (1) and Clostridium perfringens (1). All the isolates were susceptible to cefamandole. Eleven of the patients responded favorably to therapy, including the patient with typhoid fever (Table IV). One patient, a heroin addict with endocarditis due to S. aureus, continued to have positive blood cultures while being treated with cefamandole. In another patient with endocarditis due to S. aureus, cefamandole therapy was terminated on the third day because the patient developed headache and white blood cells were found on examination of the cerebrospinal fluid. Cefamandole was discontinued on the eleventh day of therapy in a

TABLE III

Minimum Inhibitory Concentrations of Cefamandole for Clinical Isolates

Gram-positive[a]			Gram-negative		
Organism	No. of Iso-lates	Mean MIC (μg/ml) (range)	Organism	No. of Iso-lates	Mean MIC (μg/ml) (range)
Streptococcus sp.	1	0.15	*Escherichia coli*	3	1.02
(α-hemolytic)					(0.75–12.5)
Strep. pneumoniae	1	0.15	*Enterobacter cloacae*	3	2.3
Staph. aureus	7	1.14			(0.78–3.12)
		(0.2–3.12)	*Citrobacter diversus*	1	5
Staph. epidermidis	6	4.6	*Hemophilus influenzae*	3	0.65
		(0.78–12.5)			(0.25–1.25)
		Disk Sens. Only	*Proteus mirabilis*	3	1.76
Clostridum sp.	1				(0.6–3.12)
			Salmonella typhi	1	0.78
			Eikenella corrodens	1	0.2
			Klebsiella pneumoniae	1	Disk Sens. only
Total	16	2.48	Total	16	1.6
		(0.15–12.5)			(0.2–12.5)

[a] Isolate of *Clostridium perfringens* was susceptible to cefamandole by disc diffusion test.

TABLE IV

Results of Therapy With Cefamandole

Infection	Number[a]	Cure (%)[b]	Failure	Side Effects
Bacteremia	15	11 (85)[e]	2	2
Pneumonia	16	13 (87)[f]	2	1
Soft Tissue	12	11 (100)[g]	0	1
Urinary	5	5 (100)	0	0
Total	48	40 (91)[h]	4	4

[a] Three patients with soft tissue infection and two patients with urinary tract infection also had bacteremia and are included in both categories.

[b] Bacteriologic cure with clinical improvement.

[c] Patients developing hypersensitivity reactions and those showing side-effects requiring cessation of cefamandole therapy were not considered cures or failures.

[d] Side effects requiring cessation of cefamandole before adequate therapy could be administered.

[e] Calculated on the basis of a total of 13 infections.

[f] One patient had responded favorably to therapy when the drug was discontinued.

[g] Calculated on basis of 11 infections.

[h] Calculated on the basis of a total of 44 infections.

patient with endocarditis due to S. epidermidis because of unexplained rise in serum urea nitrogen and creatinine. However, the patient was afebrile and had negative blood cultures; no further therapy was required. Cefamandole was discontinued after three weeks of therapy in the patient with endocarditis due to Eikenella corrodens because the patient developed fever, and decrease in neutrophil count, hematocrit, and platelets. The blood cultures were negative and the hemogram returned to normal after cessation of cefamandole therapy. However, fever recurred and the patient was treated with ampicillin and gentamicin with cure of the infection.

Respiratory Infection

Sixteen patients had pneumonia, none was bacteremic but one had bacteremia secondary to empyema. Hemophilus influenzae was isolated from two or more sputum specimens from three patients, S. aureus from 2, and E. coli from 2. No organism was isolated in nine patients with pneumonia although these patients had clinical evidence of bacterial infection including pulmonary infiltration, fever, elevated white blood cell count, and increased neutrophils and bands. In addition, these patients had purulent sputums. Cure was achieved in 13 of the 16 cases (Table IV). Two patients with infection due to E. coli were treatment failures although the organisms were susceptible to cefamandole. Cefamandole was discontinued on the third day of therapy in a patient from whom Hemophilus influenzae was isolated from transtracheal aspirates because of appearance of rash. The patient was clinically much improved when cefamandole was discontinued and the rash may have been related to topical iodine. One patient developed superinfection with Aspergillus fumigatus in a cavitary lesion. The patient with empyema did not respond and therapy was switched to another cephalosporin and an aminoglycoside.

Soft Tissue Infection

There were 12 patients with various soft tissue infections; 4 of the patients also had bacteremia. Cellulitis was present in six patients and in one was associated with osteomyelitis. Cholangitis, wound infection, pelvic inflammatory disease, external otitis with mandibular osteomyelitis, and a necrotizing oral cellulitis accounted for the other five cases. Bacterial pathogens were isolated from nine patients and included S. aureus (5), Streptococcus sp. (2), Enterobacter cloacae (2), E. coli (1), and Proteus mirabilis (1). Cure was achieved in eleven patients. Cefamandole was discontinued in one patient with mandibular osteomyelitis on the third day of therapy because of pain at the intravenous site (Table IV).

Urinary Tract Infection

Five patients with urinary tract infection were treated with cefamandole. All of the patients responded favorably including two with bacteremia (Table IV).

Side Effects

Adverse effects were encountered in eight patients and necessitated cessation of cefamandole therapy in five (Table IV). In two patients pain at the intravenous site was a prominent complaint and in one of these patients phlebitis was evident. One patient developed rash and another developed a pulmonary superinfection with Pseudomonas sp. Three patients showed rise in BUN and creatinine. One of these patients with endocarditis due to S. epidermidis was receiving 12 gm of cefamandole per day; the serum creatinine rose to 2.7 mg/100 ml but returned to normal levels when cefamandole was discontinued. Another patient was receiving 6 gm/day of cefamandole for pyelonephritis with ureteral obstruction. In this patient, it was difficult to differentiate between drug toxicity and tubular necrosis that may have followed nephrectomy. The third patient, with a history of gout, was receiving 6 gm/day of cefamandole for urinary tract infection and had a history of allergy to penicillin. The serum urea nitrogen and creatinine returned to normal levels following discontinuation of cefamandole. Two patients developed marked decrease in neutrophil count while on cefamandole therapy. The hemogram returned to normal within a week following cessation of cefamandole therapy in both patients. One patient may have had a prior allergy to a cephalosporin.

Discussion

Cefamandole proved to be very effective in the treatment of infections due to both gram-positive and gram-negative bacteria in severely ill patients with underlying diseases. The overall cure rate was 91% in this series of patients. The only disturbing side effect was leukopenia, seen in two patients who were receiving large doses of cefamandole. Other cephalosporins, including cephalothin and cefazolin, have been reported to cause leukopenia (7). Our series of patients is too small to indicate whether leukopenia will be a more frequent side effect of cefamandole, especially with large doses such as 12 gm/day.

Three patients with endocarditis due to Staphylococcus epidermidis, including an infection on a prosthetic valve, was cured of their infection. Infections due to S. epidermidis vary in response to therapy with penicillins, including β-lacatamase resistant penicillin derivatives, but are susceptible to therapy with cephalosporins (7). Of the two patients with endocarditis due to S. aureus treated with cefamandole, one continued to have positive blood cultures while on cefamandole therapy. Adequate bactericidal concentrations of the drug could not be achieved in the patient's serum. In the other patient, the drug was discontinued on the third day of therapy because of central nervous system abnormalities. White blood cells were found in spinal fluid examination although cultures were sterile. Therapy was discontinued because of the poor penetration of cephalosporin derivatives including cefamandole into the cerebrospinal fluid when tested at certain dosage regimens (8).

The patient with bacteremia due to Salmonella typhi was cured with cefamandole therapy. Isolates of S. typhi including strains resistant to ampicillin and chloramphenicol, are extremely sensitive to cefamandole in vitro (9). Thus, cefamandole may prove to be quite useful in the treatment of S. typhi infections.

Thirteen of the 16 patients with pneumonia responded favorably to cefamandole therapy and 13 were considered as cured. Of the three patients with Hemophilus influenzae pneumonia, two were cured and the other had responded favorably when therapy was discontinued. Cefamandole should prove useful in the treatment of Hemophilus influenzae pneumonia in patients hypersensitive to ampicillin and perhaps even in patients with organisms resistant to ampicillin.

All of the bacterial isolates were susceptible to cefamandole. Peak blood levels achieved with cefamandole were more than twice the MICs of the least susceptible isolates found in this study. The serum concentrations achieved with cefamandole are much higher than those obtained with cephalothin (5, 10). The concentrations of cefamandole found in bile are greater than those achieved with cephalothin but lower than those of cefazolin (11). Cefamandole diffuses well into interstitial fluid (11). The drug was well tolerated when administered either intramuscularly or intravenously. Only two patients complained of pain at the intravenous site and only one had phlebitis. These problems are common with all cephalosporins (7).

Cefamandole appears to be a safe, well tolerated cephalosporin derivative with a broad spectrum of antibacterial activity that can be administered either intramuscularly or intravenously. The drug can be used in situations where broad spectrum coverage including H. influenzae is required. It should be especially useful in the treatment of infections due to Hemophilus influenzae and also S. typhi.

Summary

Cefamandole is a new cephalosporin derivative with a broad spectrum of activity against both gram-positive and gram-negative bacteria. Patients with either bacteremia, pneumonia, soft tissue infection, or urinary tract infection were treated with cefamandole. The patients were suffering from various underlying diseases. The overall cure rate was 91%. Neutropenia occurred in two patients. The drug was well tolerated by either intramuscular or intravenous route.

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Clinical Approaches to Calculous Biliary Tract Disease: Third Annual Leon Ginzburg Lecture

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In approximately 90% of patients with calculous biliary tract disease, the calculi are composed primarily of cholesterol. The metabolic derangement of etiologic significance in this condition is the presence of a relative excess of cholesterol in relation to the solubilizing lipids in bile, viz., phospholipids and bile salts. In the remaining 10% of patients with cholelithiasis, the stones are composed of bile pigments and other breakdown products of hemoglobin metabolism.

Historical Perspectives. The general course of events in man's conquest of his diseases has followed a rather consistent pattern. First, there has been the discovery and description of pathology; second, the definition of the alterations of physiology; and third, the correlation of these with the clinical manifestations and the complaints and symptoms of the patient. In this respect, the earliest description of biliary concretions is to be found in the works of Alexander Trallianus, a Greek physician of the fifth century, who noted calculi within the hepatic radicals of a human liver. Many centuries, however, elapsed until Vesalius in the sixteenth century recognized that biliary calculi represented a disease process.

The first successful surgical cure of this disease was not accomplished until July 15, 1867. On this date, Dr. John S. Bobbs of Indiana operated upon a 30-year-old woman with an abdominal mass presumed to be an ovarian tumor. It was not until after he had incised a huge hydropic gallbladder that he realized the true nature of the lesion present. After evacuating the contents of the gallbladder, he sutured it closed. The patient's postoperative course was uneventful, and she lived to old age without recurrence of her symptoms. Total removal of the gallbladder, however, was not attempted until 15 years later, i.e., in 1882. It was successfully accomplished by Carl Langenbuch of Germany. Four years hence, cholecystectomy was first performed in the United States by Justus Ohage of Minnesota. Now, less than 100 years later, approximately 400,000 patients are operated upon annually in the United States for biliary tract disease, the vast majority of whom are suffering the consequences of calculous disease.

Clinical Material. At the New York Hospital-Cornell Medical Center, there has been a sustained interest in improving the care and treatment of patients with calculous biliary tract disease. This has been achieved in large measure by the careful documentation of the nature of the disease process as well as

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the long-term results of surgical therapy. The compilation of this data reflects the life-long interest and dedication of Dr. Frank Glenn, my teacher, and in recent years, coinvestigator.

In the years 1932 through 1975, there were 10,479 service patients operated upon for nonmalignant biliary tract disease. Cholecystectomy was performed in 8,077 patients; cholecystostomy, 373; and choledochotomy plus cholecystectomy or cholecystostomy in 1,500. Secondary choledochotomy, usually in search of stones, was performed in 311 patients. Operative procedures for the correction of strictures and miscellaneous conditions were carried out in 218 patients.

During the 42-year span of this study, 9,794 patients were operated upon for acute or chronic cholecystitis. The relative proportion of patients operated upon for acute cholecystitis has decreased from 25.02% in the years 1932 to 1939 to 13.3% in the years 1970 to 1974. This decrease reflects improvements in the early diagnosis of calculous gallbladder disease, particularly by radiography, and an increasing acceptance of elective surgery.

Of major significance with respect to this patient population is the increasing proportion of patients 65 years and older. In the early years of this study (1930's), only 4.5% of the patients were in this age group. More recently (1970's), 27.4% of the patients were 65 years of age or older. Clearly, this was the most important determinant of operative mortality. Of the 4,847 patients under 50 years of age, there were 19 deaths, an operative mortality of 0.4%. In the age range of 50 to 64 years, there were 63 deaths among 2,596 patients operated upon, a mortality rate of 1.8%. In patients aged 65 years and older, there were 19 fatalities among 4,847 patients, a mortality rate of 5.1%.

It is convenient to consider this group of 10,479 patients in two categories, namely, those with chronic or nonacute biliary tract disease and those with acute inflammatory disease.

Chronic Biliary Tract Disease. There were 8,392 patients operated upon for nonacute disease with an operative mortality of 1.3%. The operations performed and the mortality rates associated with them are as follows: cholecystectomy, 6,588 patients, 0.5% mortality; cholecystostomy, 82 patients, 8.5% mortality; choledochotomy combined with cholecystectomy or cholecystostomy, 1,193 patients, 4.3% operative mortality; secondary choledochotomy, 311 patients, 2.9% mortality; operations for common duct strictures and miscellaneous conditions, 218 patients, 8.3% mortality.

There are many factors responsible for the low operative mortality associated with elective cholecystectomy. I would emphasize, however, the importance of technique and the careful and accurate identification of the structures in the hepatoduodenal ligament. Every effort must be made to carefully identify the cystic artery, cystic duct and common duct before initiating the dissection to remove the gallbladder.

Cholecystostomy was performed infrequently for nonacute biliary tract disease. This procedure was most often reserved for those patients with serious associated medical illnesses, and this is reflected in the high operative mortality for this group of patients.

Acute Biliary Tract Disease. Twenty percent or 2,087 patients in this series presented with acute cholecystitis. The overall operative mortality for this group of patients was 3.5%. Age and the severity of the inflammatory process were the major determinants of mortality. The operative mortality rate for 533 patients 65 years and older was 9.2%. In contrast, the mortality rate for 1,554 patients less than 65 years of age was 1.5%. In the 1970's, 40% of the patients operated upon for acute cholecystitis were 65 years of age or older.

In patients with acute cholecystitis, cholecystostomy may be performed in preference to cholecystectomy if there is inflammatory obliteration of the anatomic landmarks which are requisite for safe cholecystectomy. In this context, cholecystostomy is a reflection of the severity of the acute cholecystitis. Cholecystostomy performed in 291 patients had an operative mortality rate of 9.2% whereas cholecystectomy was accomplished in 1,489 patients with a mortality rate of 1.3%. Choledochotomy, in conjunction with cholecystectomy or cholecystostomy, was performed in 307 patients with an operative mortality rate of 8.4%.

One of the major areas of controversy in biliary tract surgery, and in particular acute cholecystitis, concerns the appropriate time for surgical intervention. Some surgeons, including myself, prefer early operation, and others, delayed surgical intervention.

While it is true that many patients can and do recover from their acute episode of cholecystitis, it is equally true that some do not resolve despite appropriate antimicrobial therapy. The sequence of events in those patients who fail to respond to conservative therapy is the progression of cholecystitis to first gangrene and then perforation. Calculi obstruct the cystic duct, and this is followed by bacterial infection of both the wall and contents of the gallbladder. With progression of this inflammation, there is thrombosis of the cystic artery with first gangrene and then perforation.

In an effort to determine the frequency of perforation, I have collected from the literature and our series at The New York Hospital 26,334 cases of acute cholecystitis (Table I). The incidence of perforation in this collected series is 10%. The mortality from perforation in this group of patients is 21.3%. At The

TABLE I

The incidence and mortality rate of perforation of the gallbladder in patients with acute cholecystitis. Published reports and the experience at The New York Hospital-Cornell Medical Center.

Source (year)	Number studied	With perforation (%)	Mortality rate
Diffenbaugh (8) (1949)	5,272	629 (12%)	24%
Strohl (9) (1962)	7,708	647 (8%)	19%
Friley (10) (1972)	2,069	157 (8%)	27%
Rosoff (11) (1973)	58	4 (7%)	25%
Salleh (12) (1974)	218	9 (4%)	0%
McDonald (13) (1974)	65	7 (11%)	14%
Gagic (14) (1975)	93	5 (5%)	100%
New York Hospital (15) (1971)	851	93 (11%)	8%
TOTAL	26,334	1,553 (10%)	21.3%

New York Hospital, there were 93 perforations amongst 851 patients with acute cholecystitis, an incidence of 11%. Perforations of the gallbladder have been classified by Niemeier (1) into three types. Type 1, perforation into the free peritioneal cavity, occurred in 15% of the patients in The New York Hospital series. Type 2 perforations, evidenced by pericholecystic abscess, occurred in 40% of the patients; and type 3 perforations, into adjacent viscera, occurred in 45% of the patients. Unfortunately, it is usually impossible to predict which patients with acute cholecystitis will progress to perforation and also to diagnose perforation preoperatively. It is these concerns which prompt me to advocate early operation in patients with acute cholecystitis.

In general, patients with acute cholecystitis should be approached with dual objectives: 1) correction of the metabolic deficits resulting from the disease process itself or the presence of associated conditions; and 2) confirmation of the diagnosis. In most patients, these objectives can be accomplished within 24 to 48 hours. With respect to confirmation of the diagnosis of acute cholecystitis, we have been impressed by the increasing usefulness and accuracy of ultrasonography. The reliability of this study is such that the incidence of false positive examinations is very low. The traditional and still useful methods of confirming the diagnosis of acute cholecystitis involve radiographic techniques such as plain films of the abdomen and intravenous cholangiography.

Mortality and Morbidity of Biliary Tract Surgery. The mortality rates associated with the various biliary tract procedures as well as some of the risk factors have been outlined. In order to place these statistics in perspective, we have analyzed the causes of death and morbidity for 3,115 consecutive patients subjected to 3,217 operations for the period of 1950 through 1966.

During this 16-year period, there were 63 postoperative fatalities. The most frequent cause of death was cardiovascular complications which occurred in 29 patients. There were 14 deaths related to the hepato-biliary tract, primarily cirrhosis. Of the 13 deaths related to infection, 5 occurred in patients with subphrenic abscess, 5 were secondary to complications of antimicrobial therapy and 3 were due to peritonitis or gas gangrene of the abdominal wall. There were 5 deaths in patients with preexisting renal disease.

There were 260 nonfatal complications in 221 patients, a morbidity rate of 7%. Slightly more than one-half, or 140, of these complications were extrabiliary, and 120 or 46% were directly related to the biliary tract.

Pulmonary complications, pneumonia and atelectasis, occurred in 67 patients and lead the list of extrabiliary complications. Cardiovascular complications occurred in 31 patients, 20 of whom had myocardial infarctions. Thirteen of these 20 patients had no history of heart disease and normal pre-operative EKG's. Urologic complications, infection and/or retention, occurred in 26 patients, and there were 16 additional miscellaneous complications.

The most frequent complication directly related to biliary tract operations was infection. There were 62 wound infections, 7 subphrenic abscesses and 6 drain site infections. Seven patients had postoperative pancreatitis and 5, cholangitis. Bleeding of sufficient magnitude to require transfusions occurred in 7 patients, 2 of whom required reoperation for hemorrhage from the stump of the cystic artery. In 2 patients, there were problems related to retained T-tubes.

The complication which is of paramount importance to the surgeon, perhaps because it reflects to some extent upon his technical skill, is the retained common duct stone. There were 24 instances of this complication. The majority, 14 of the 24 patients, had undergone cholecystectomy and choledocholithotomy. Three patients had had cholecystectomy plus cystic duct cholangiograms, and 2 patients each had been subjected to cholecystectomy with negative common duct exploration, cholecystectomy alone, and excision of cystic duct remnant. One had undergone a secondary choledochotomy for retained stones. This study points out the obvious fact that the patients at highest risk to have retained common duct stones are those operated upon for common duct stones. For the years 1932 through 1974, the incidence of retained common duct stones was 4.5% of those patients who had undergone cholecystostomy or cholecystectomy plus choledochotomy. Considering the total number of biliary tract operations performed during this period, 10,008, the incidence of overlooked common duct calculi was 0.96%.

Postcholecystectomy Symptoms. Much has been written about symptoms referable to the abdomen in patients who have had operations upon the biliary tract. In some patients the cause of these symptoms has not been apparent, and they have often been labeled as having the postcholecystectomy syndrome. An exact definition of this syndrome has never been proposed or widely accepted by the medical profession. Because of the lack of agreement concerning this syndrome, we sought to define in some concrete manner the causes of abdominal symptoms in patients previously subjected to biliary tract operations. We chose as our end-point patients who required additional intraabdominal surgery after cholecystectomy. To accomplish this, we analyzed the records of 5,859 patients who had had cholecystectomy. In this group, 253 or 4.5% had a secondary abdominal operation. Certainly this was not all the patients who had a continuation or appearance of new symptoms following operation. These were, we believe, the ones who had severe symptoms following definitive biliary tract operations.

Approximately two-thirds, or 166, of these patients were operated upon for disease of the liver, biliary tract or pancreas and one-third, or 87 patients, were operated upon for disease conditions in other intraabdominal organs. Of the patients with disease of liver, biliary tract and pancreas, 102 were operated upon for common duct problems. In almost all of these patients there were retained calculi. Cystic duct remnants were excised in 57 patients, and six were operated upon for pancreatitis or carcinoma of the pancreas. One patient had an open liver biopsy for cirrhosis.

The importance of this study is that it pointed out the hazards of ascribing symptoms in patients who have had biliary tract surgery to the postcholecystectomy syndrome, an entity which many of us believe does not exist. The study also suggests that prime consideration be given to disease of the common duct in evaluating patients with new or persistent symptoms following cholecystectomy.

Asymptomatic Gallstones. An area of mutual concern to both internist and surgeon alike is the management of the patient with silent or asymptomatic gallstones. As a rule, internists favor conservative or nonoperative therapy for these patients; surgeons generally advocate cholecystectomy. Statistics are available to support either position. In actual practice, it is the patient who usually makes the final decision, and, in my experience, he rarely accepts cholecystectomy in the absence of symptoms. It is important, however, in dealing with such patients to know the natural history of "silent gallstones".

Despite the fact that this subject is frequently discussed, there are few reports of patients who have been carefully evaluated over a long period of time. Wenckert & Robertson (2) followed 781 patients for an average of 11 years; Comfort, Gray & Wilson (3) reported on 112 patients followed up to 20 years; and Lund (4) studied 526 patients followed for 5 to 20 years. The remarkable observation in these reports is the consistent finding that approximately 50% of the patients developed symptoms, usually within 5 years of the finding of gallstones. Serious sequellae such as acute cholecystitis or obstructive jaundice occurred in 20% of the patients.

The principal consideration that prompts surgeons to recommend elective cholecystectomy is operative mortality. Patients undergoing elective cholecystectomy have an operative mortality of 0.3 to 0.5%. Patients operated upon for acute cholecystitis have a mortality rate at least fivefold greater, viz. 2.5 to 5%. Furthermore common duct stones are almost never found in patients with asymptomatic calculi in the gallbladder whereas they are present in 20% of the patients who are symptomatic.

Interpretation of this data will vary dependent upon one's personal experience. My own approach to patients with silent gallstones is to review this information with them, and in the absence of significant associated medical illnesses, recommend cholecystectomy.

Hyperplastic Cholecystoses. The term "hyperplastic cholecystoses" was introduced by Jutras & Levesqué (5) in 1960 to encompass a group of benign lesions of the gallbladder characterized by excessive proliferation of its normal tissue components. These lesions include:

A) Adenomyomatosis
B) Cholesterolosis
C) Neuromatosis
D) Lipomatosis
E) Fibromatosis
F) Hyalinocalcinosis

The etiology of these entities is unknown, but some are probably congenital such as adenomyomatosis, neuromatosis and fibromatosis. Others, such as cholesterolosis and hyalinocalcinosis, are possibly metabolic in nature. These lesions are to be differentiated from true papillomas of the gallbladder, which are neoplastic lesions with malignant propensities.

The role of the hyperplastic cholecystoses in producing symptoms of biliary dysfunction is unresolved. In formulating a clinical approach to patients with these lesions, it is important to recognize that they are asymptomatic in some patients, while in others they give rise to symptoms identical to those produced by calculi. Cholecystectomy is reserved for those patients with symptoms. However, before proceeding with surgery, these patients should undergo a complete investigation to exclude other disease which may mimick gallbladder disease. In carefully selected patients, the long-term results of cholecystectomy are good.

Chronic Acalculous Cholecystitis. Physicians are often perplexed when confronted with patients complaining of symptoms suggestive of disease of the gallbladder and in whom the conventional oral cholecystogram is normal. After a thorough GI evaluation, these patients are often considered to be psychoneurotic or are referred to a surgeon for consideration of cholecystectomy for so-called chronic acalculous cholecystitis. The vast majority of surgeons are justifiably skeptical of this diagnosis and will not recommend cholecystectomy in the absence of radiographic proof of disease in the gallbladder.

Our approach to these patients has been greatly influenced by studies of the acalculous gallbladder at The New York Hospital (6). From 1932 to 1942, 1,050 cholecystectomies were performed, and of this group, 71 patients or 6.8% had no calculi in the gallbladder. From 1943 to 1954, the incidence of acalculous gallbladders removed had fallen to 2.9%. Since 1954, very few cholecystectomies have been performed on patients with radiographically normal cholecystograms.

Histologic examination of the 71 gallbladders removed from 1932 to 1942 revealed chronic cholecystitis in 52, cholesterolosis in 4 and no disease in 15. Of the 49 gallbladders removed from 1943 to 1954, 39 were believed to exhibit sufficient inflammatory infiltrate to warrant a diagnosis of chronic cholecystitis, five disclosed cholesterolosis, and 5 were normal.

The results of surgery in this group of patients were disappointing. Of the group operated upon from 1932 to 1942, only 63% were considered to have had a good result; 14% had a fair result; and 23% a poor result. Patients operated upon from 1943 to 1954 had equally disappointing results. These statistics deterred us from recommending cholecystectomy in patients with symptoms of gallbladder disease and normal cholecystograms.

In the 1960's, efforts to improve the results of surgery in patients with suspected chronic acalculous cholecystitis received impetus from the introduction of cholecystokinin cholecystography. This technique permits the radiologist to document the response of the gallbladder to cholecystokinin stimulation. Following the intravenous injection of cholecystokinin, serial cholecystograms are obtained. These x-rays are examined for evidence of disordered contractile response such as persistent spasm of particular segments of the gallbladder. There is, however, no concensus amongst radiologists as to the criteria sufficient to distinguish the normal from the diseased gallbladder. The major contributions to the literature by authors advocating this technique to identify chronic acalculous cholecystitis are listed in Table II. These studies were deficient in their lack of appropriate controls, and the technique of cholecystokinin cholecystography has not been widely accepted.

A carefully controlled, critical evaluation of cholecystokinin-cholecystogra-

TABLE II

*Cholecystokinin-cholecystography. Favorable reports from the literature with the number of patients examined by this technique, operated upon and improved or cured of their symptoms. * N.A (not available). ** 12/14 (of the 14 followed 12 were improved).*

Authors	No. of patients studied	No. operated	No. improved
Nathan (16)	141	70	66
Goldstein (17)	40	25	NA*
Nora (18)	24	24	12/14**
Valberg (19)	13	12	12
Cozzolino (20)	7	7	7

phy was reported by Dunn et al (7) in 1974. This group studied both asymptomatic controls as well as patients with symptoms suggestive of gallbladder disease. In addition, the radiologists interpreted the cholecystograms without knowledge of the patient's symptoms. The conclusions from this study were that the radiologists could not identify the response of the normal gallbladder to cholecystokinin nor could they predict the histo-pathology of the gallbladder on the basis of the roentgenograms. There was no relationship of cholecystokinin induced abdominal pain to the results of cholecystectomy. In addition, some patients not operated upon had an unexplained improvement in symptoms.

At the present time, my approach to patients with symptoms of gallbladder disease and with a radiographically normal gallbladder is to carefully evaluate these patients in terms of other possible causes of their abdominal complaints, see them at sufficiently frequent intervals to convince myself that these complaints are legitimate, and only then consider cholecystectomy. I do this with the knowledge of the limitations of the oral cholecystogram which, in the best of hands, has an accuracy of ±97%. In these carefully selected patients, pathologic examination of the gallbladder often discloses small calculi or lesions such as cholesterolosis.

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Announcement

A week-long course in Human Endocrinology will be held October 30–November 3, 1978 at Lenox Hill Hospital, New York City. The emphasis will be on female endocrinopathies, menstrual disturbances, thyroid and adrenal diseases, and andrology. The course is under the directorship of Lenox Hill Hospital physicians Herbert S. Kupperman, M.D., Ph.D., and Hugh D. Melnick, M.D. The cost of the course is $350 for physicians and $200 for residents and medical students. For more information, contact: Dr. Hugh D. Melnick, Department of Obstetrics and Gynecology, Lenox Hill Hospital, 100 East 77 Street, (212)794-4096.

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Sterile Breast Abscess in a Heroin Addict

MARIAN WAXMAN, M.D.

Abstract

A young woman addicted to heroin developed a sterile breast abscess in the injection site, simulating clinically a solid mammary neoplasm. This new facet of narcotic addiction, heretofore unreported, should be thought of in a differential diagnosis of breast lumps.

The ingenuity of drug addicts in search for new sites of injection knows no limits. After most of the peripheral veins have been used up, the addict "mainliner" (injecting drug intravenously) becomes a "skin popper" (injecting drug subcutaneously). A wide variety of skin lesions associated with the subcutaneous injection of narcotics in drug addicts have been described (1). The intramammary injection of heroin by a drug addict, with a subsequent development of a breast abscess, has not been reported previously to our knowledge.

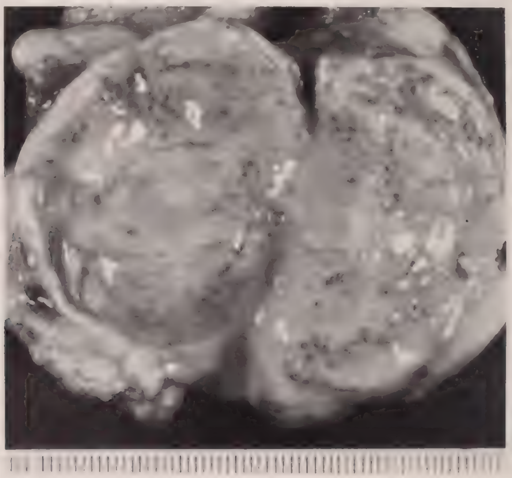

FIG. 1. Gross appearance of the breast abscess.

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Case Report

The patient was a 27-year-old black woman, hospitalized because of a breast mass of one-year duration, with an admitting diagnosis of fibroadenoma, carcinoma to be excluded. She admitted being a former heroin addict and alcoholic. She had a history of nephrotic syndrome diagnosed

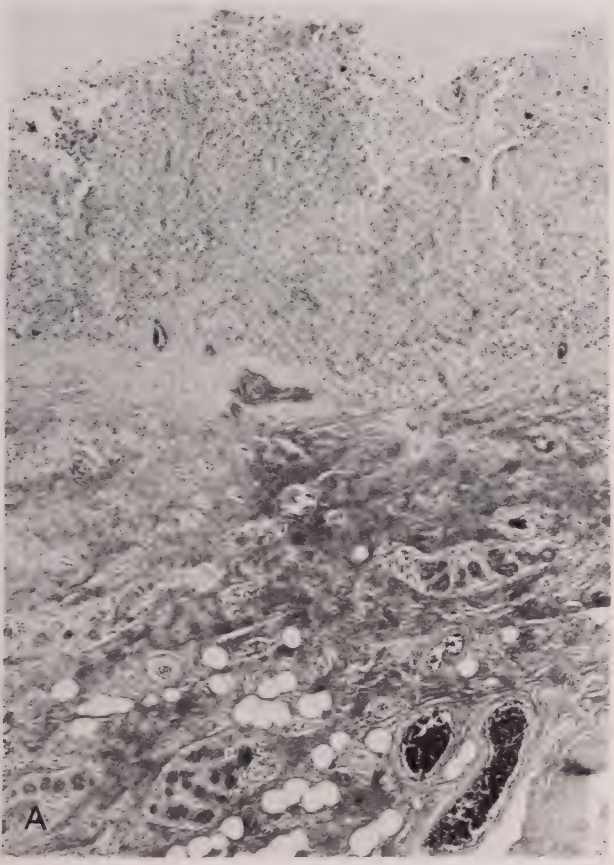

FIG. 2. A. Photomicrograph of the abscess wall showing the breast tissue with a few dilated blood vessels (bottom), fibrous abscess wall, and a chronic inflammatory exudate lining the cavity (top) (H & E, ×30) B. Details of the inflammatory exudate and granulation tissue photographed under polarized light, and revealing several doubly refractile starch crystals (H & E, ×120).

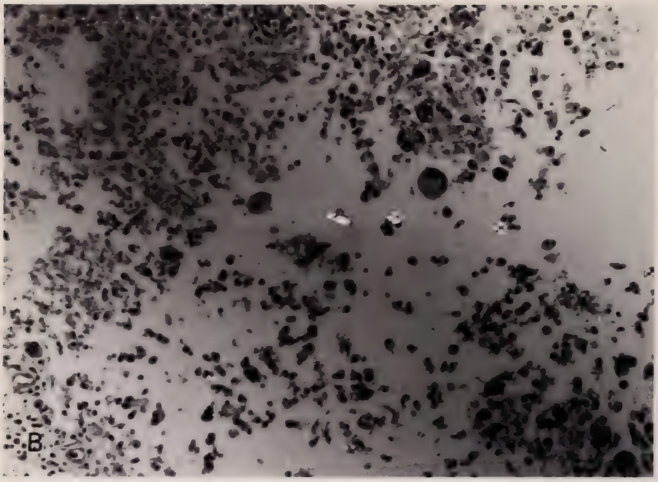

FIG. 2. B.

nine years previously, and a hypertension, for which she took no medications. The history included appendectomy at the age of 10, and two cesarean sections, six and five years prior to her present admission. The patient stated that one year previously she injected heroin into her left breast, and subsequently noted a mass at precisely the same location. The tumor was occasionally painful and apparently had not changed in size during the year.

Her blood pressure was 140/90 mm Hg, temperature 98.6F, and pulse 72 beats per minute and regular. The left antecubital fossa displayed old needle marks, and the veins in this area were thickened and sclerotic. A mass was palpated in the upper inner quadrant of the left breast. It was described as firm, movable, and 5 × 4 cm in size. There were no associated skin deformities, and no masses were felt in the opposite breast. The axillary lymph nodes were not enlarged. The remainder of the physical examination was described as normal. Blood count and urine analysis were normal. SMA—12 chemical determinations yielded normal values, except for an elevated creatinine (2.4 mg%) and a slightly elevated LDH (330 IU). Electrocardiogram, X-rays of the chest and the bone survey were normal.

The breast mass was excised under general anesthesia revealing a thin-walled cavity filled with a brown, semisolid material (Fig. 1). Microscopic examination showed an abscess surrounded by a rim of normal breast tissue. The cavity was lined by chronic inflammatory tissue containing numerous histiocytes, foamy macrophages and plasmocytes (Fig. 2A). A number of doubly refractile starch granules were seen under polarized light within the inflammatory exudate (Fig. 2B). Culture of the abscess contents revealed no growth.

Comment

Subcutaneous abscess was the most common complication among "skin poppers" in a series described by Hussey and Katz (2). In their 102 cases of narcotic addicts, 68 showed one or more abscesses. In all patients in this group, but two, the drug used was heroin. Other authors have also noted frequent occurrence of this complication (1, 3–5). Our review of the literature failed, however, to reveal a description of a patient who used the breast as a repository for a narcotic injection.

Abscess in the non-lactating breast is a rarity in itself (6). Ekland and Zeigler (7) have collected 50 such cases. Most of their patients were of premenopausal age, and Staphylococcus was the most frequently isolated causative organism.

Lesions resembling clinically breast abscess seen in the non-lactating woman can represent duct ectasia, chronic recurrent infection associated with metaplasia of the lining epithelium, or a carcinoma (6). In our patient, the cystic nature of the lesion was not appreciated before the surgical exploration, and she was thought to have a solid breast neoplasm. The formation of the abscess was indubitably caused by the local necrotizing effect of the narcotic, or of one of the admixed substances, analogous to the effect on the nasal mucosa described previously in cocaine users, and only recently recognized also in heroin addicts (8).

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Idiopathic Diabetes Insipidus Occurring in a Patient with Turner's Syndrome

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JUDITH WILLNER, M.D.

Abstract

A case of idiopathic diabetes insipidus occurring in a patient with Turner's syndrome is presented. The patient had an XO karyotype in addition to exhibiting many of the characteristic stigmata of Turner's syndrome. The presence of diabetes insipidus was documented by the effect on urine osmolarity of water deprivation followed by an injection of aqueous vasopressin. The patient's serum prolactin was elevated with normal adrenal and thyroid functions. There was no evidence of a pituitary or hypothalamic tumor on tomography of the sella or computerized tomography of the brain. One additional case of diabetes insipidus occurring in a patient with Turner's syndrome has been documented in the literature. A possible relationship between these two entities is discussed.

The association of Turner's syndrome with diabetes insipidus has not been previously reported in the English literature. Turner's syndrome is not generally considered to be associated with abnormalities of the hypothalmus or pituitary gland. One case has been reported of a patient with Turner's syndrome who developed an FSH-secreting adenoma (1); diabetes insipidus was not present. Recently, a patient was described in the Bulgarian literature with Turner's syndrome and complete diabetes insipidus (2). We wish to describe a second such patient.

Case Report

The patient was a 32-year-old Caucasian female admitted to The Mount Sinai Hospital for endogenous depression. Three months prior to admission the patient had noted the sudden onset of polyuria. There was no history of head trauma or neurologic disorders. She denied dysuria and urine cultures were repeatedly negative. Additional history included lack of normal breast development and the presence of oligomenorrhea since puberty. The latter portion of the patient's history was disputed by her mother, who claimed that her daughter had never menstruated. The patient was taking no medication.

After intelligence testing at the age of ten, the patient had been classified as mildly retarded; with special tutoring she was able to obtain a general high school diploma by the age of twenty. One year prior to admission, the patient underwent a formal IQ test. Her verbal score was 81 with a performance score of 64; perceptual motor incoordination was noted.

Physical examination revealed a tense, withdrawn woman in no acute distress. She was normotensive and eumetabolic. Her height was 4'11" with moderate kyphoscoliosis and an increased carrying angle. The fourth and fifth metacarpals of the hands appeared short. Scattered across the face and trunk were numerous pigmented nevi. The posterior hairline was low set. The ears had normal configuration and were not low set or rotated. There was a small amount of facial hair present. Visual fields and fundoscopic examination of the eyes were normal. She had a high

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arched palate with normal dentition. There was no webbing of the neck but the chest was shieldlike with pectus excavatum. Breast development was at Tanner stage 1. Cardiovascular examination, including femoral pulses, was normal. The genitalia were unambiguously female with pubic hair development at Tanner stage 3. Brawny, non-pitting edema was present in the lower extremities, especially on the right where there was 2+ pretibial and pedal edema.

The patient underwent a dehydration test under continual supervision; the results, shown in Table I, conclusively demonstrate the presence of diabetes insipidus (3). The remaining endocrine tests are reproduced in Table II. Thyroid function is normal and there is probably normal adrenal reserve. The ovarian axis demonstrates the classic lack of feedback inhibition seen in Turner's syndrome. Serum prolactin is approximately 50% above the upper limit of normal, an abnormality not previously noted in Turner's syndrome. Routine blood chemistries including fasting blood sugars were normal.

A buccal smear was chromatin negative. Karyotyping of a metaphase preparation of the patient's peripheral lymphocytes revealed a 46, XO complement in all 20 cells examined (Fig. 1).

The patient's skull x-ray, reproduced in Fig. 2, shows a normal sized sella turcica with an apparent "double floor"; this "double floor" was felt to represent pneumatization of the sphenoid sinus. Tomography of the sella failed to reveal erosive changes. Computerized tomography of the brain was normal. An IVP revealed bifid, flabby pelves.

Discussion

This patient demonstrated many of the typical stigmata of Turner's syndrome, including short stature, short fourth and fifth metacarpals, pigmented nevi, increased carrying angle, low posterior hair line, a high arched palate,

TABLE I

*Water Deprivation Test**

Time (military)	Urine			Blood		Weight (kilograms)	Comment/medication
	Volume (ml)	Osmolarity (mOsm/l)	Na (mEq/l)	Osmolarity (mOsm/l)	Na (mEq/l)		
1010	500	43	7	292	145	37.5	Void volume
1100	270	44	7				
1200	260	58	9	306	148		
1300	175	66	10				
1400	160	92	10	307	148		
1430							aqueous Pitressin 5 units s.c.
1500	80	138	13				
1530	12	268	23				
1600	15	356	26			35.9	

* Water deprivation from 0800 till conclusion of test.

TABLE II

Basal (Morning) Hormone Values

	Plasma cortisol (μg/100 ml)	Plasma estradiol (ng/ml)	Serum FSH (mIU/ml)	Serum prolactin (ng/ml)	Serum thyroxine (μg/100 ml)	Resin triiodothyronine uptake (RT$_3$U)
Patient	23	0.93	43.3	31.5	9.8	1.07
Normals	10–25			0–20	4.5–13.5	0.85–1.15
Normal menstruating females		3.0–50.0	2.7–7.4			
Normal postmenopausal females		0.6–2.2	26.5–63.7			

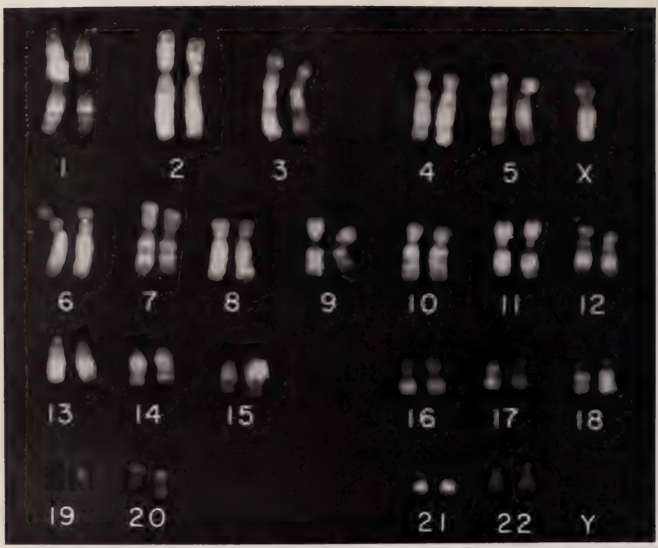

FIG. 1. Karyotyping of a metaphase preparation of the patient's peripheral lymphocytes.

pectus excavatum with broadly spaced nipples, retarded sexual development, and a renal anomaly (4-7). The typical webbing of the neck seen in this syndrome was absent as were various cardiovascular anomalies, including coarctation of the aorta. Osteoporosis with kyphoscoliosis as seen in this patient was undoubtedly a consequence of life long estrogen deprivation. Results of the patient's intelligence testing demonstrated a relatively high verbal score together with poor spatial perception such as is classically seen in Turner's syndrome (8-10) The lymphedema present in this case is usually seen in adult patient's with Turner's syndrome only after estrogen replacement is initiated (11). Perhaps the patient had greater estrogen production than suggested by her plasma estradiol; her history of oligomenorrhea rather than amenorrhea may have been correct.

In addition to Turner's syndrome, she manifested diabetes insipidus. While Turner's syndrome is a common chromosomal anomaly with an incidence amongst newborn phenotypic females of 0.37 per thousand (12), idiopathic diabetes insipidus is a rare entity (13). The concurrence of these two diseases has been noted once previously in the medical literature (2). The patient was a 17-year-old Bulgarian girl evaluated in 1971 in Sophia. She was amenorrheic. Polyuria and polydypsia had been noted since the age of 13. On physical examination she presented with many of the classic stigmata of Turner's

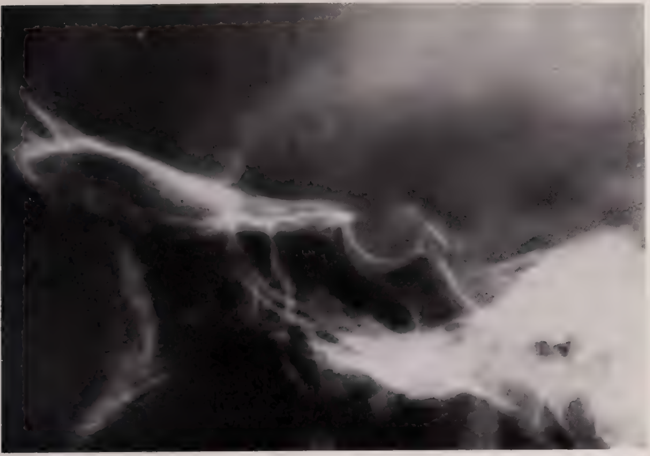

FIG. 2. Lateral skull x-ray.

syndrome including female sexual infantilism and short stature. Her karyotype was 46, XO. During a five day period while hospitalized, she excreted from 11 to 17 liters of urine per day. Results of her CBC and chemistries, including a GTT, were normal. During a Carter Robbins test, she continued to excrete hypotonic urine while receiving hypertonic saline; 45 minutes after the start of a hypertonic saline infusion her urine specific gravity was 1.002 at a flow rate of 20 ml/minute. She then received a vasopressin injection followed by a marked increase in urine concentration; within 45 minutes of the injection her urine specific gravity was 1.015 at a flow rate of 1.7 ml/minute. Thus there was good documentation in this case of both Turner's syndrome and diabetes insipidus. Additional hormonal evaluation of the patient revealed normal thyroid function and borderline adrenal function (17 KS of 16.5 mg and 18.2 mg per 24 hours and 17 OH of 2.2 mg and 1.2 mg per 24 hours respectively).

Our patient's elevated prolactin together with a double-floored sella turcica suggested, of course, the presence of a pituitary tumor. If such a tumor were large enough, or strategically placed, it could have accounted for her diabetes insipidus through interference with the release or production of antidiuretic hormone. That pituitary enlargement and even tumor can arise from a lack of estrogen feedback suppression on the ovarian axis is a well documented though uncommon occurrence (14-16). One case of an FSH-secreting pituitary adenoma has been reported in Turner's syndrome; however, diabetes insipidus was not a part of the presentation and plasma prolactin was not measured. In addition, the documentation of that tumor's presence, which consisted of an enlarged sella on plain skull film, was also consistent with the presence of an empty sella syndrome occurring fortuitously. In our patient no evidence of erosive changes was seen on tomography of the sella and computerized tomography of the brain did not reveal the presence of a pituitary or hypothalamic tumor.

The addition to the medical literature of a second case of diabetes insipidus occurring in a patient with Turner's syndrome suggests that there may be an association between these two entities. A reproducible intellectual defect, poor spatial perception, is now well documented in Turner's syndrome which implies that other CNS defects, including those of the hypothalmus may exist in such patients.

The meaning of our patient's elevated prolactin is uncertain. She suffered from endogenous depression, but was not taking any medication. Elevated levels of basal prolactin have been reported in endogenous depression; however, serum prolactin levels distinctly above the upper limits of normal are not commonly seen in such patients in the absence of psychotropic medication (17-19). Elevation of gonadotropins with hyperresponsiveness to LRF is well documented in Turner's syndrome (20). Whether elevated levels of prolactin and hyper responsiveness to known stimulators of prolactin occurs in Turner's syndrome, remains to be investigated. The presence of diabetes insipidus and elevated prolactin in our patient may indicate a common defect in the hypothalmus.

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Mycosis Fungoides with Pulmonary Manifestations

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Mycosis fungoides is an uncommon lymphoma which begins in the skin and occasionally spreads to other organs. This dissemination is now known to be more common than was once believed (1), but reports of patients with visceral involvement and gross evidence of pulmonary infiltration are rare (2–4). For this reason, we wish to present the following case:

Case Report

J. J., a 51-year-old white male veteran first discovered a skin problem in October 1973, erythematous, scaly, asymptomatic lesions over his upper chest. A private physician initially diagnosed the disease as "psoriasis," and no treatment was given for one year, when severe pruritus developed. After another year of ineffectual topical therapy, a skin biopsy was taken, which revealed unequivocal mycosis fungoides. By this time there were nodular lesions and plaques over the scalp, face, thorax, and limbs (Fig. 1). Chest x-ray showed only a small, rounded nodule in the left lung field consistent with granuloma.

Whole body electron beam therapy was begun in the first three months of 1976 at another hospital. The patient was finally referred to us in November 1976. At this time chest x-ray showed multiple nodular densities in both lung fields (Fig. 2). There were no systemic symptoms, and 3,000 Rads of 120 KEV x-ray was administered to reduce the size of discrete skin lesions, with good result.

On 2/1/77, the patient was readmitted to our hospital complaining of weakness and a dry cough. His temperature was 98.6°F and vital signs were normal. The chest film was unchanged. There was no palpable lymphadenopathy and no hepatosplenomegaly. The hematocrit was 40 and white blood cell count was 6,100. The SMA 18, intravenous pyelogram, liver scan, and bone scan were normal.

Pulmonary function studies were performed on 2/9/77. These revealed marked reduction of lung volume. Diffusion capacity by carbon monoxide single breath method was also diminished. The maximal mid-expiratory flow rate was normal. All of these findings were considered compatible with restrictive lung disease.

On 3/15/77, the patient's temperature rose to 102°. Intermediate PPD was negative, as was fungal culture of sputum. Bacterial culture revealed coagulase positive staphylococci. A transbronchial lung biopsy performed through a fiberoptic bronchoscope revealed large clusters of abnormal cells consistent with mycosis fungoides; this was confirmed on electron microscopy (Fig. 3). Fungal stains of this material were negative. The fever failed to respond to Keflin and Kanamycin. Chemotherapy was therefore begun with cytoxan, but the patient continued to deteriorate and expired on 3/27/77. Shortly before death, his arterial blood gases revealed pH 7.43, pCO_2 23 mmHg, pAO_2 mmHg (on respirator).

Permission for postmortem study could not be obtained.

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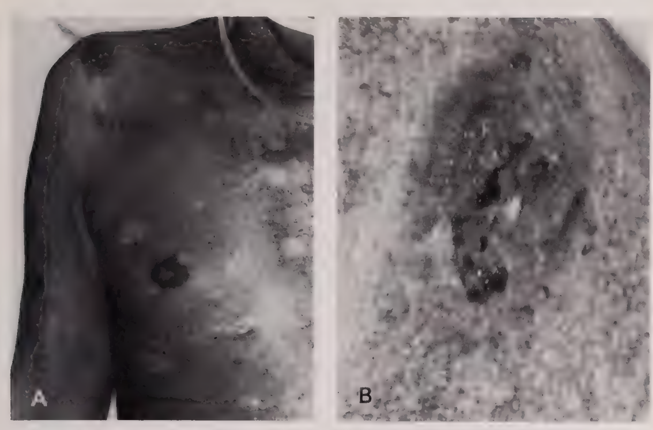


FIG. 1. A. Patient's trunk demonstrating typical lesions of mycosis fungoides. B. Close-up view of a single mycosis fungoides lesion.

Discussion

Mycosis fungoides has been known as a distinct disease entity since the first description by Alibert (5) in 1806. During the past century, the disorder has been interpreted as having both a neoplastic and an inflammatory origin. Today most pathologists agree that the etiology is truly a malignant proliferation of lymphoid and reticulum cells.

Mycosis fungoides has long been recognized to progress to fatal malignant lymphoma (6). Debate, however, still persists as to the histologic characteristics in the advanced cases with extracutaneous involvement.

Reports from some older studies indicate that there is transformation of these extracutaneous cases into histiocytic lymphoma, lymphocytic lymphoma, or Hodgkin's disease (6–8). But more recently, extracutaneous dissemination has been observed to be a clinicopathologically distinct phase in the natural history of the disease, with no transition to a different type of malignant lymphoma (2). The distinguishing microscopic feature is the heterogeneity of cell types comprising the infiltrate—pleomorphic mycotic cells interspersed among many inflammatory cells. Despite considerable variation in the cutaneous infiltrates, the histologic character of extracutaneous disease is quite distinct from Hodgkin's disease and malignant lymphoma of lymphocytic or histiocytic type (9).

Gross involvement of the lungs by mycosis fungoides is uncommon. Of six cases treated since 1959, only the present one has shown such involvement. Of Rappaport's 32 cases (3), 13 were reported to have gross tumor, though no

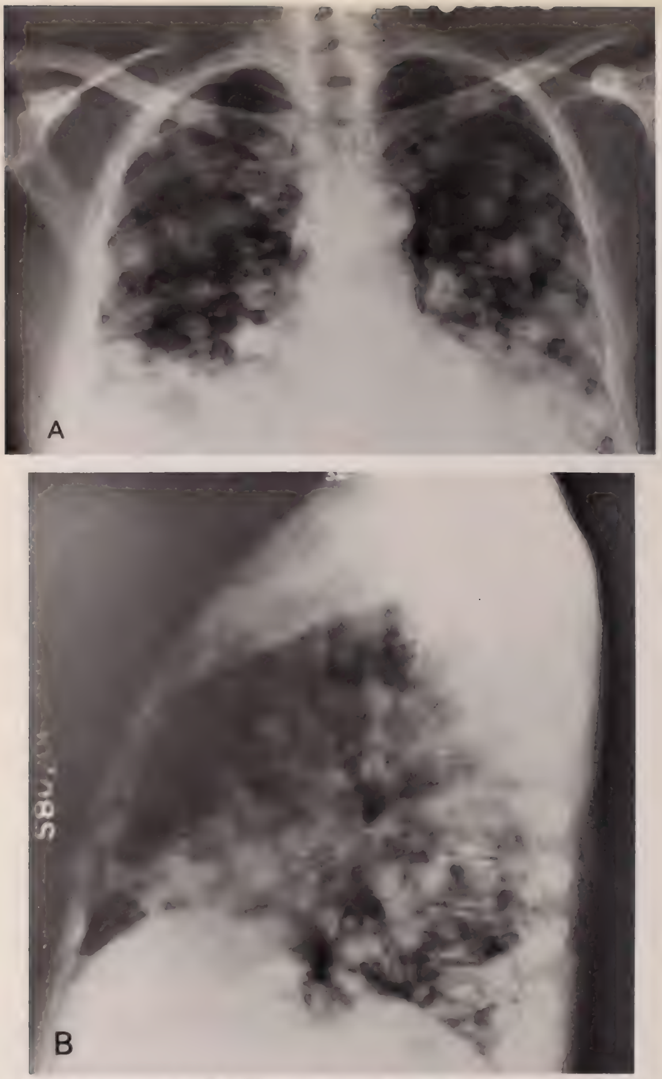


FIG. 2. Radiographs of chest showing multiple round densities that are pulmonary infiltrates of mycosis fungoides.

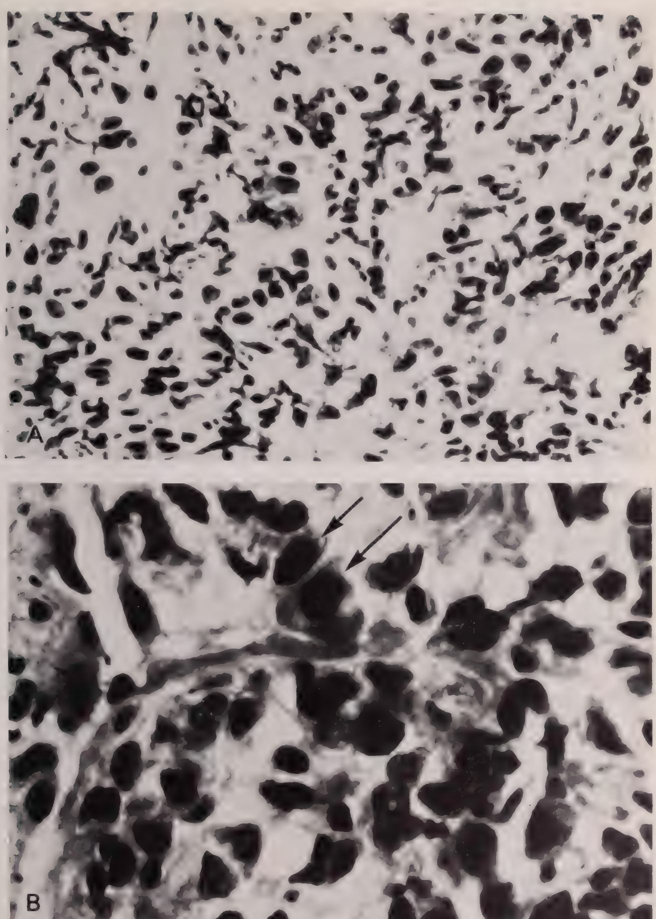
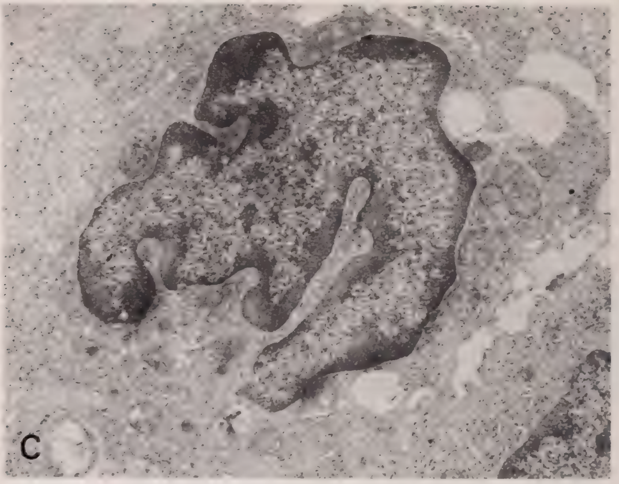


Fig. 3. A, and B. Low and high power microscopic views of transbronchial biopsy specimen. Note the pleomorphic cellular infiltrate containing mycosis fungoides cells (arrows). C. Electron micrograph of a representative area shows these cells to have highly convoluted nuclei and cytoplasm with scanty organelles. These findings are characteristic of mycosis fungoides.



mention of pulmonary radiographic changes was made. Long reports eight of fifteen patients with pulmonary involvement at autopsy, but does not comment on gross involvement (2). In Cyr's series of 23 cases with no transformation to another form of lymphoma before death, only four showed pulmonary involvement, though again no comment was made as to whether this was gross or microscopic (4).

It is not easy to differentiate pulmonary mycosis fungoides radiographically from other conditions, but we feel that the absence of fever and other constitutional manifestations, as well as the normal blood picture, strongly suggest neoplasm rather than infection. Our patient was free of constitutional symptoms for at least two months before his rapid downhill course began. However, a long period of survival cannot be expected once the lungs have become involved.

In retrospect, we probably should have undertaken to treat the patient with supervoltage beam therapy to his chest, employing total lung fields for a tumor dose of 1500–2000 rads, with daily fractions of 150 to 200 rads. An appropriate alternative is moving strip therapy for the total lung field to tumor dose of 2100–2800 rads. Mincer and her colleagues have used this technique on a total of 85 patients with advanced metastatic pulmonary lesions. These patients were significantly benefited, symptomatically and objectively, and pulmonary function improved in most cases as treatment progressed (10).

Summary

A case of pulmonary involvement by mycosis fungoides is presented. Once the disease had progressed to this stage, there was a rapid downhill course.

Radiation therapy to the chest might be a valuable adjunct in the treatment of such patients.

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Admissions to Medical School: Refining the Issues

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Abstract

Admission to medical school is often viewed as an arbitrary and capricious process, with large numbers of well-qualified applicants unable to pursue a medical career increasing each year. Analysis of data pertaining to the admissions process reveal interesting findings. Over the past several years the size of the applicant pool has begun to decrease. College seniors applying to medical schools for the first time represent only 40% of the applicant pool and have an overall acceptance rate of 47%. For those students with a B average or better, acceptance rates were considerably higher. Undergraduate grade point average (GPA) and Science Medical College Admissions Test scores (SMCAT), however, are not the sole factor in the admissions process. Students were admitted with widely discordant GPA's and SMCAT's. American students who have performed well in a foreign medical school are being accepted in increasing numbers into the American medical educational system, either with advanced standing or upon completion of their undergraduate training through Fifth Pathway programs or direct entry into the National Intern and Residency Matching Program.

Although the number of students entering the study of medicine continues to increase each year, considerable pressure further to increase enrollment is exerted upon schools of medicine both from public and private sectors. Charges of capricious and arbitrary behavior by admissions committees continue unabated, at times accompanied by cries of reverse discrimination.

Critics are quick to point out the large number of "qualified" applicants compared to the available positions; the inflexibility of the admissions process with respect to an undue reliance on objective parameters; the inability of admissions committees to evaluate the potential for achievement in medical school; the disinterest of these committees in accommodating those American students studying medicine abroad, and the insufficient attention of the admissions process toward those students more inclined towards primary care rather than research or specialization.

The public's demands have found responsive legislatures on both federal and state levels. The Health Professions Educational Assistance Act of 1976 (PL 94-484) emphasized the need for medical schools to devote attention to primary care (1). In addition, for the first time, encroachment on the actual admissions process was legislated, with the Secretary of Health, Education and Welfare being given the authority to assign, with advanced standing, American medical students in foreign medical schools who pass Part I of the National Board Examinations to American medical schools. Recently, this section of PL 94-484 was amended to allow for a greater degree of discretionary action on the part of admissions offices.

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Selection of students for medical school is certainly far from perfect. There is little evidence of any existing criteria predictive of an individual's ability to become a concerned and competent physician. Yet the results of the admissions process rarely have been analyzed in journals, other than those devoted to educational issues. In view of the persistent concern over the ability of medical schools to meet the perceived needs of society, several issues pertaining to medical school admissions will be reviewed to attempt to more clearly refine some of the existing problems.

Acceptance-Applicant Ratios

From 1964 to 1974, the number of applicants to medical school has consistently increased. However, in 1975, for the first time in ten years, the number of applicants declined by 321 (1%) compared to the preceding year (2). The number of applicants for places in the 1976–1977 class similarly decreased by 1% over 1975 (3). On the other hand, the number of enrolled first-year students continued to increase (Table I), with first year enrollments for 1977–1978 up to 3.3% over the preceding year and 18% since 1972. Total enrollments over this six-year period rose by 27%. The number of medical schools also rose during this period from 112 to 120, with several additional schools in an active planning stage and proposals submitted for six more, two located in Puerto Rico (4). In spite of these increases in enrollment, the total number of applicants to the 1976–1977 class was impressive, 42,155, with only 37.4% of total applicants accepted (2).

These figures have led to the charge that each year an increasing number of well-qualified applicants are turned away from medical school, thus not being able to pursue a medical career. A further analysis of these data, however, is warranted. Of the 42,155 applicants to the 1976–1977 class, approximately 33% represented repeat applicants to medical school. An additional 23% of applicants represented either students who had not yet completed four years of undergraduate training or had received their undergraduate degree at least one year prior to filing application. Undergraduate seniors seeking admission to medical school for the first time (in phase students) represented only 40% of the applicant pool. The acceptance rate of these students was considerably higher (47% vs. 31%).

When analysis with respect to grade point average (GPA) and Science Medical College Admission Test scores (SMCAT) is performed, further variations in acceptance rates are discovered. These data are available for the class

TABLE I

	First Year Enrollments	Total Enrollments
1972–1973	13,677	47,366
1973–1974	14,159	50,751
1974–1975	14,763	53,554
1975–1976	15,295	55,818
1976–1977	15,613	57,765
1977–1978	16,136	60,039

entering 1975–1976. Of those in phase students receiving a GPA of 3.0 or above, with SMCAT's of 500 or above, 57.5% of these candidates were accepted for entry to medical school (5).

The selection of a GPA of 3.0 (B average) as a minimal criterion in assessing a student's chance of gaining admission is arbitrary but it is unlikely that one would not accept a B as a minimal criterion for acceptance to medical school. Among applicants for the 1975–1976 entering class, a GPA of 3.0 or greater was seen in 65%. The proportion of students with GPA's of 3.6 or above represented 42.2% of the applicant group in 1974, increasing considerably since 1970, when 19.7% of applicants achieved a 3.6 or above (6). Indeed, one might well argue that a 3.0 GPA in our current educational milieu is too low a standard in assessing ability to master the medical curriculum. Although this impressive rise in A and A− grade point averages among applicants may represent a better qualified applicant pool, other factors, such as grade inflation, may also play a role.

Data with respect to undergraduate grading are hard to obtain. It is a general consensus of educators, however, that a grade inflation is a persistent reality, with several major universities acknowledging that 65–70% of their students make the Dean's List (7). Available data from the senior colleges in The City University of New York in 1974, which, in the presence of open admissions, did not experience a grade inflation, reveal that 34% to 40% of all undergraduate students received a B or better in Biology and Chemistry (8).

Suslow at the University of California at Berkeley, however, in a review of grading policies at eight universities found that from the early 1960's to the early 1970's, the percent of A grades awarded more than doubled (16% to 34%), while the percent of C grades diminished by not quite half (37% to 21%).* A major reason given for this inflation was the increased competition for entry to graduate and professional programs.

It is, therefore, perhaps rather conservative to suggest that a minimum degree of scholastic competency should be agreed upon with respect to capability for performing work and that a GPA of 3.0 represents the minimum degree of scholastic competency required.

If one reviews data pertaining to students who have a GPA above 3.0, the data are even more encouraging. The acceptance rate of those applicants to medical school for the 1975–1976 entering class receiving an average of B+ or better, regardless of SMCAT scores, is also considerably higher than the 36% overall acceptance rate, being 56% of all such applicants and 63% for in phase students. Of these students with SMCAT scores in the 80th percentile or above, acceptance rates are 60% and 72%, respectively, for all and for in phase students. If one would define a superior student as one with a GPA of 3.3 or above, with SMCAT scores in the 700's, the acceptance rates of these individuals range from 84% to 92% (5).

These data suggest that superior students, as defined by SMCAT scores and GPA, stand an excellent chance of acceptance into medical school. Even students who are considered to be "solid" stand a better than 50-50 change of acceptance.

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* Suslow S, Office of Institutional Research, University of California, Berkeley, February 1976.

Variability of Acceptance Criteria

Students who excel in examinations will not necessarily make the best physicians. Of equal importance is the question as to whether academic achievement is used as the sole criterion for acceptance to medical school. Data pertaining to the class entering 1975–1976 would appear that such was not the case. Students who received A− and B+ averages, with SMCAT's of 600 and above, had acceptance rates as low as 65% (5). On the other hand, applicants with GPA's of 2.3 to 2.99 (B− and C+) and SMCAT's in the 500's and up had acceptance rates of 17% to 35%. Even some applicants with GPA's of 2.0 and SMCAT scores in the 400–500's gained acceptances to medical school, albeit with much less frequency than the general applicant pool, ranging from 9% to 18%. These data would suggest that parameters other than GPA and SMCAT scores are reviewed by admissions committees in providing admission to medical school.

Another charge leveled against admissions committees is that individuals with majors in the sciences are given undue preference with respect to admission to medical school. In this regard, data from the applicant pool of the class of 1975–1976 is pertinent (9). Of the total applicant pool for this year, there were a considerable number of individuals (75%) who majored in biology, chemistry, zoology, psychology, premedicine, or biochemistry, with the number of students majoring in other nonscience areas representing less than 19% of the total applicant pool. The percent of applicants accepted, however, in each field did not differ greatly. Thus, although 34% of students majoring in biology and 43% of students majoring in chemistry who applied to medical school were accepted, acceptance rates of 34% in political science, 49% in philosophy, 45% in anthropology, 43% in foreign language, and 41% in English occurred. The highest acceptance rates were seen in students participating in honors programs (76%) and interdisciplinary programs (53%). It may be true that those individuals in the nonscience fields applying to medical school were perhaps better qualified than the general pool of applicants in biology and chemistry. Unfortunately, however, these data are not available and in any rate should not militate against the equally successful acceptance rate observed with liberal arts majors.

Other factors have been implicated in affecting the admissions process. The recent rise in tuition for medical school has been accompanied by the fear that acceptances would be offered to relatively few low-income students as compared to students residing in a high socioeconomic income bracket. This belief is not unwarranted as the increasing individual costs of financing medical education have outstripped general cost of living increases and, considering the accompanying decrease in federal capitation, may still continue to soar. However, before conclusions can be drawn concerning the effect of family income on admissions, one must assess family income of all undergraduate students as the medical school applicant pool is only drawn from those students who complete the required college programs. An analysis performed by the AAMC, based upon income data from the 1974–1975 academic year, revealed that the low income range (annual income under $10,000) encompassed 36% of all American families, 19% of families with students in their third or fourth year of college, 15% of families with medical school applicants, and 12% of families with medical school acceptees (10). Among all levels of income, the greatest disparity was between the income of all US families and families of third- and fourth-year college students rather than between medical school applicants and acceptees. These data do, however, indicate that medical schools accept slightly smaller percentages of lower income students and slightly larger percentages of students with high family incomes, although the major factor in the selection appears to be the prevailing family income of those students who reach their junior year of college and decide to apply to medical school. Although there has been an increase in available loan funds, unfortunately medical school tuitions do not appear to be reaching a plateau. Interest rates are not inconsiderable, and many students from lower economic backgrounds are particularly hesitant to commit themselves to what is rapidly becoming a considerable financial burden. Existing scholarships, associated with "pay back" provisions for practice in underserved areas, are being avidly sought after by many students. It remains to be determined if these remedies will be sufficient to attract lower income students to apply to medical school.

Outcome of Nonaccepted Students

There are, however, many students in college who intend to go to medical school and are initially unable to gain acceptance into an American medical school. In an attempt to provide insight into the numbers and types of these students, a study performed by Baird concerning careers and curricula of undergraduate students is of interest (11). This study was based on a follow-up of a national sample of 21,000 college seniors who replied to a questionnaire mailed in the Spring of 1971. The distribution of sample colleges was close to national averages on environmental scales developed by Astin (12). The ability of students to achieve career goals a year after graduation revealed some surprising results. Those students who planned to study the arts or the humanities and the social sciences least often followed through with their plans, with 34.5% and 38.6%, respectively, actually entering these areas. Slightly more than half the students who had planned to study biological or physical sciences, business or other fields actually entered their intended vocation. Those students who planned to enter law school or medical school, however, followed through with their plans more often than any other group (70.8% and 75.2%, respectively). Only 24.8% of those students who had planned to go to medical school were not in medical school. If one analyzes these data with respect to undergraduate grades and percentage of students engaged in planned activity a year later, of those students achieving B or A averages, 69% to 93.4% were engaged in medical school a year following the survey. Even 42% of those students who had undergraduate GPA's of C or below actually had gained admission into medical school. These data, although less recent than those cited from the Association of American Medical Colleges (AAMC), tend to corroborate the former, indicating that a student need not perform in an outstanding or even superior manner to gain acceptance to medical school, and correspondingly, undergraduate grades are often not the sole criterion for admission.

Since GPA's and SMCAT's certainly cannot provide exclusive criteria as to the success of completing a medical curriculum or, what is more relevant, becoming a compassionate physician, many students with less than average objective parameters may still be capable of successfully completing medical school. If a considerable number of students do not gain immediate admission to an American medical school and yet most of these students do eventually enter medical careers, the most obvious routes are either through repeat application to a US medical school or entry into a foreign medical school.

American Students in Foreign Medical Schools

It is difficult to determine the precise number of students enrolled in foreign medical schools. However, this number is increasing each year and probably exceeds 8,000. Recently several foreign medical schools have specifically solicited American student enrollment, either through working arrangements with placement agencies in this country or direct advertising in the press. Although many foreign medical schools offer good academic programs, several of these schools exist in name only and may be actively engaged in defrauding American students (13).

The cost of obtaining this medical education varies considerably, depending on the individual school. In view of the rising tuition in this country, however, even at the most expensive foreign schools, there are American medical schools whose costs currently are comparable or considerably higher, with several schools charging annual tuition ranging from $6,000–$12,500. Although the costs for entering medical school in Europe are considerably less than those in this country, unfortunately there are many students not able to afford the luxury of going to a foreign medical school who might have been eligible for financial aid if they were accepted in an American school. These students should not be forgotten. Since almost all students who successfully complete the medical curriculum will practice medicine in the United States, it would be worthwhile for the government to consider making National Health Service Scholarships available to these students while attending an approved foreign medical school.

The desirability of Americans entering foreign medical schools may be viewed in several ways. The student is forced to leave the American educational system and undertake training in an environment that is different culturally and educationally and has a considerably greater student-faculty ratio. In many instances a new language must be learned. If the student remains for the entire four years, the clinical training that will be obtained is also markedly different from that received in US medical schools. On the other hand, the liberal admission policies of many foreign medical schools have allowed students who were underachievers in college or who were unable to gain admission to an American medical school to prove their ability to handle the medical curriculum. These students then have the chance to enter the American medical system either with advanced standing or upon completion of their formal medical education.

Students in foreign medical schools may be accepted with advanced standing into the third year of an American medical school, either directly by a school or by sponsorship through the Coordinated Transfer System (COTRANS) of the Association of American Medical Colleges, with subsequent admission by a medical school. The numbers of students applying through COTRANS increased since the program's inception in 1970 until recently when the numbers of applicants started to decline. A summary of COTRANS activity for the years 1970–1974 reveals 3,844 applicants took Part I of the National Board Examinations. Of this number 1,044 (31.1%) passed and 826 (79%) were accepted with advanced standing into US medical schools (14). In 1976, of the 852 applicants, 459 (54%) passed Part I. A total of 458 students transferred with advanced standing to the second or third year in US medical schools (3, 15). These data, however, are not representative as an increasing number of American students studying abroad have opted to take the National Boards under individual school sponsorship rather than through COTRANS. For example, in 1977, although 1,224 applicants were sponsored through COTRANS, a total of 2,137 examinees sat for Part I, with slightly less than 50% achieving a passing score.* Of this group of passing students, 564 were unable to be admitted with advanced standing to an American medical school.** The number of schools admitting these students has progressively increased from 38 in 1970 to 63 in 1977. The number of students admitted has similarly risen. These data suggest a continuing commitment by medical schools to American medical students studying outside of the country.

The need for these students to enter foreign medical schools in the first place is often questioned when two to four years later a large number will reenter the American medical educational system. If those students accepted with advanced standing were divided among existing US medical schools, each school would have to admit less than four students in the first year class. Since approximately two-thirds of COTRANS candidates have already been rejected from an American medical school, one problem with this suggestion is the inability of admissions committees to identify this relatively small group of students out of approximately 27,000 applicants who did not gain admission.

Over the past six years the majority of American students enrolled in foreign medical schools have not been able to pass Part I of the National Board Examinations, the failure rate ranging from 40% to 71%. Over the past four years the percent of COTRANS examinees taking the examination more than once has varied from 12% in 1972 to a high of 40% in 1975, with pass rates of first time examinees consistently under 50%.***

Many have assailed the Part I Examination as being unfair since, over the past four years, only 40% to 60% of American students in foreign schools have successfully completed this examination. This compares with a pass rate of 85–90% for students in US medical schools. Not all students in US medical schools, however, are required to take the Part I Examination or even to record a passing score in order to advance to the third year. This has been regarded by some as a double standard, prejudicial against those students studying in foreign schools. Unfortunately, the educational process at many of these schools differs markedly from the American educational system. A common denominator is essential to compare competency in the basic sciences of these students with their peers in US medical schools. Although one may criticize the use of Part I as a minimum criterion for acceptance, some standard must be set, and it does not appear that this examination is an unreasonable requirement.

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* Data provided by the National Board of Medical Examiners.

** HEW News Release, November 18, 1977 Health Resources Administration.

*** Data provided by the AAMC Division of Student Studies, November 1977.

The frustration of these students studying abroad is understandably great, and the impact that this has had on the Federal level has been considerable. The recently passed PL 94-484 specifically included a section requiring all medical schools applying for capitation to accept assignment of American students studying abroad who had passed Part I but did not receive an acceptance to an American medical school. Not surprisingly, this provision met with a great deal of resistance from both undergraduate and graduate universities as a severe infringement on the admission process. Subsequent discussion by all concerned groups resulted in a repeal of the provision without a diminution of the commitment of Congress to help those individuals previously enrolled in a foreign medical school to reenter the American educational process.

Of those students unable to gain admission with advanced standing to US medical schools, entry into the graduate American medical educational systen can occur after completion of formal course work, receiving the M.D., and successfully passing the qualifying examination of the Educational Council of Foreign Medical Graduates (ECFMG). Recently an increasing number of American students have been enrolled in schools that require one or more years of social service or internship prior to awarding the M.D. Not infrequently, the educational value of this experience is far from optimal. In an attempt to accommodate these students, the American Medical Association, since 1971, has sponsored, and many states have endorsed, a program providing a year of supervised clinical training at an American medical school. Successful completion of this program, (termed the Fifth Pathway), allows the student to enter the National Intern and Resident Matching Program (NIRMP) and to apply for state licensure in those states endorsing this track. There are in excess of 300 students currently enrolled in a year of supervised clinical training at US medical schools (16). Evidence indicates that the success rate of these students in obtaining graduate training programs through the NIRMP is comparable to those students receiving the M.D. from a US medical school (17).

Facilitation of reentry of these students, however, has paradoxically resulted in an increasing number of students flocking to medical schools out of the country, predominantly in the Caribbean. Several schools have surfaced which are clearly interested solely in financial gain and provide the student with little or no medical training (13). Although the legislative mandate concerning Americans studying medicine abroad clearly was directed only at students enrolled prior to 1976, it has been misinterpreted by many as an encouragement to enroll in a foreign medical school. Hopefully, increased publicity concerning this problem will result in a greater awareness and caution on the part of those considering this route.

The Racial Minority Student

The dilemma confronting admissions committees with respect to the racial minority applicant is considerable. The Federal government has provided multiple regulations and policies concerning affirmative action. The AAMC has also lent strong support to the development of affirmative action plans to recruit minority students into medical school. Minority groups have been rightly vocal about the need for greater representation of minorities in medicine. Criticism has also been leveled at the perceived undue reliance placed by admissions committees on grades and SMCAT scores. The medical schools have attempted to respond to these needs. From 1968–1969 to 1971–1972, the number of black freshmen in medical school tripled (18). Over the past four years the percentage of total enrolled racial minority students has increased, but only modestly, from 8.3% in 1973 to 10.4% in 1974, 10.6% in 1975, and 10.9% in 1976. Total "underrepresented" US minority enrollment in all four years of American medical schools has increased from 6.6% in 1972 to 9% in 1977,* still far short of the 15% representation of these groups amongst the general population (3, 19).

The stability of the proportion of minorities entering the first year class over the past several years, however, does not indicate the lack of effective affirmative action. In the 1974–1975 entering class, black Americans represented only 5.6% of the applicant pool but 7% of all acceptees, with an acceptance ratio of 43.3% as compared with an overall average ratio of 35.3% ($p=0.05$). Similar findings existed for other minority groups (American Indian 48%; Mexican Americans 49%; Mainland Puerto Rican 43%) (20). The difficulty appears to rest with an inability to increase the applicant pool of minority candidates rather than with indifference on the part of admissions committees.

In the Fall of 1974, a survey of 189,000 full-time college freshmen revealed 59,706 (31.5%) to name medicine as their career choice. A comparison with data obtained in 1966 revealed the greatest increase in interest in medicine to be among women (132%) and blacks (102%). In spite of this increase, however, 91.5% of students aspiring toward medicine were nonblack, even though the percentage of nonblack men choosing medicine as a career decreased by 2.4% since 1966 (21). There are undoubtedly many reasons for the plateauing of minority applicants to medical schools. Although ineffective information concerning health careers, lack of preparation in both secondary schools and colleges, fear of discrimination in medical school, medical school attrition rates, and ease of entry into less demanding professions are major areas of concern, the overwhelming factor appears to be the increasing cost of obtaining a medical education, associated with a relative decreasing availability of funds (21–23). Bruhn and Hrachovy found 91% of 212 black undergraduate students to feel inadequate financial assistance to be the most important factor in limiting minority applications to medical schools (22).

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* Data obtained from Division of Student Studies, AAMC, November 4, 1977.

Even when financial aid is adequate, however, the other factors come into prominence. Successful black medical school applicants decide early in their careers to become physicians. Affirmative action programs on a medical school level, although essential, occur far too late to influence the applicant pool. Undergraduate attrition of black students, compared to white, is high (24). Programs that prepare minority students at the primary, high school, and college level are mandatory if an increased minority applicant pool is to be realized.

These figures concerning minority enrollment have been interpreted somewhat differently by others to suggest that far from ineffective affirmative action, admissions committees are selecting minority students who may not have the potential for medical school, implying a moral as well as constitutional wrong. This feeling has been most publicized by the article by Davis (25) and also by the recent decision of the California Supreme Court in Bakke vs. the University of California (26). In attempting to review whether or not such adverse feelings are justified, data with respect to the 1975–1976 entering class is of interest. Of the 15,295 entering students, 1,391 (9%) consisted of underrepresented racial minorities. Available data comparing GPA's or SMCAT's on the basis of self-description of these students with the general applicant pool does reveal somewhat lower mean figures for both parameters. However, even if one would a priori assume, as critics do, that no minority student had a GPA of greater than 3.29, then minority students represent only 38% of the 3,615 students admitted with a GPA of 3.29 or below (5). This suggests that not only do criteria other than GPA's play a role in the admission process but that majority students also are benefactors of the system by at least a 2:1 numerical ratio as compared to racial minorities.

The Student and Primary Care

The need for provision of primary care is considered to be an acute and pressing problem. In the past the feeling has been that this need could only be accomplished through an absolute increase in the number of physicians, with a correspondent increase in physician-population ratio.

The physician-population ratio has grown over the past ten years, now approximating 174 per 100,000. This figure is exceeded only by West Germany and Austria among the Western developed countries and is considerably greater than the United Kingdom and Sweden, which are frequently described as having achieved their desired goals in medical care (27, 28). The lower physician-population ratios in these two countries is not surprising. The ratios considered optimal by six large prepaid groups in the United States serving approximately 3,000,000 have also been calculated to range from 100 to 130 physicians per 100,000 population (29).

Considering the present expansion of entering students in American medical schools noted above, even if the number of entering students does not increase and the current inflow of foreign medical graduates abates, by the year 2000 there will be an increase of 20% in the physician-population ratio which will place it in excess of 210 per 100,000. This may have absolutely no effect on distribution of medical care, although the total cost of health care will surely increase. It should be remembered that New York State, which has a physician-population ratio exceeded only by Israel and the USSR, still records serious shortages in medical care (30). Toward this end, prior health manpower bills passed by both the Senate and the House contained provisions for a mandatory increase in size of classes as a condition for Federal capitation. Fortunately, as a result of considerable hearings, Congress has realized that a mere increase in the number of physicians is not prudent, quite costly, and probably would not effect a change in physician maldistribution to any great extent.

How may the admissions process influence the development of primary care physicians? Evidence exists that one approach which will have a minimal effect is to select those undergraduate students who profess an interest in primary care specialties. Unfortunately, 50–75% of all students who indicate a career preference upon entering medical school will change their minds by the time they reach their senior year (31–33). There does appear to be an association between an individual's home residence and one's ultimate practice location. Programs that have recruited applicants from rural or underserved areas have found that such students are more likely to return to these areas upon completion of training (34, 35). More attention devoted to such applicants, who represent under 17% of the applicant pool, by schools serving such communities is warranted (36).

The need for more optimal medical services in many areas has been recognized by Congress and is addressed in the Health Professions Educational Assistance Act (1). This legislation expands the number of National Health Scholarships (which are associated with a service clause), establishes desired goals for primary care training programs within schools of medicine and affiliate institutions, and encourages the development of physician extenders. Evidence exists that the incentive and scholarship approach may be effective. Retention rates of physicians staying in the National Health Service Corps beyond their two-year commitment have increased impressively. In 1973, only 3% of physicians and dentists were retained, in 1974 20%, and 1975 26%. Estimates are that in 1976, 30% of National Health Service Corps medical personnel will remain beyond a two-year period (37).

Even without Federal legislation, however, support for increases in primary care physicians has been forthcoming from both schools and students. An AAMC survey in 1973 indicated that 50% of all medical centers had developed ongoing programs in family medicine, with 50% of the remaining schools intending to establish such programs shortly (38). Herman and Veleski, in a study of 969 alumni from 1971–1975, found the percentage of graduating students selecting family medicine grew each year from 6% in 1971 to 17% in 1975, with the proportion of students entering all programs dealing with primary care increasing from 46% to 55% ($p<0.03$) over the same period (39). It is of interest that this percentage already exceeds the goals established in the Educational Health Professions Assistance Act for 1980. It is quite likely that this law, combined with the existing increase in student enrollment and the needs and goals of currently enrolled students, will more than alleviate the existing shortage of primary care physicians over the next ten years.

Conclusion

The medical school admissions process is far from perfect. The excessive number of applicants makes it difficult to preceptively assess those students who will become competent physicians or engage in the clinical practice of medicine in areas most needing medical care. Working within these constraints, however, admission to medical school by qualified applicants is not as difficult as perceived nor is it solely dependent upon GPA or SMCAT scores. Foreign medical schools provide a resource for committed students unable to gain acceptance into a US medical school. Almost all of these students who complete the medical curriculum and pass the appropriate examinations will reenter the American medical educational system after two to four years to participate in residency training. Continuing curricular changes and Federal support will result in a sufficient number of primary care physicians. Attention should be focused by admissions committees on increasing the applicant pool of those groups who are underrepresented as physicians as well as devising better techniques for assessing one's compatibility for the practice of medicine. Complacency about admissions should not be a prevailing attitude—but then neither should despair.

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Philanthropy under Siege*

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Hospital development means a planned program for the improvement of facilities and services to perform laudable and realistic goals. Its success is dependent upon a well-conceived and carefully implemented development program which includes a planning component and a public relations component. There can be public relations without development, but not the reverse. Yet often there is insufficient coordination among the various forces necessary to conduct a successful development program which is designed to:

a. Build and preserve the image of the institution.
b. Plan for short- and long-range goals.
c. Emphasize to the public and the legislators the need for new or replacement facilities and services to meet the changing health requirements of the communities it serves.
d. Actually raise the money to accomplish the development program of campaign goals.

What can be done about the hospital's image and the need for obtaining nonoperating funds for retention of services and replacement of outmoded facilities? Hospitals have been caught in the mesh of the latest fad, "consumerism," and we need to rebuild our image. The answer is not simple. Patient gratification is still the keystone of a sound development program for the Hospital. It is a question where the institution places its emphasis. The focus should definitely not be on a campaign to raise money for hospital operations per se. Rather, the public must be made aware of ways by which the hospital is striving to maintain its excellence. If the hospital is a teaching institution, it must inform its public that it has always been the fountainhead of the best, the newest, and the safest in medical care treatment. Great institutions like Mount Sinai are great precisely because they attract philanthropic support. Indeed, philanthropic investments in great measure founded many of them. Advances made in American medicine are to a great extent the result of a historic symbiotic relationship between philanthropy and medical science. Philanthropy created the institutions and supported their growth. As our hospitals grew, they attracted better and brighter physicians and research scientists. Significant contributions to the future of American medicine were being made even as essential care was being provided for patients with the kinds of complicated illnesses that required the most sophisticated and ultra-specialized services. The interplay between philanthropy and medical science's advance and the delivery of health care is one of the healthiest and most

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natural relationships to be found in American society. The specialized physician is given the capacity to deliver the sort of intensive care needed by relatively few people at any moment and the donor receives the advantage of being able to give his money where he knows it will do the most good. In a sense, the philanthropic dollar is the venture capital of American medicine.

Somebody has to be able to risk mistakes—a position which government officials are not likely to accept. Our occasional mistakes are proof that we continue to try new and venturesome things. Without this sort of intelligent, conscious risk-taking, American medicine will stagnate and eventually decline. Particularly under a national health insurance plan, this environment must be maintained and *this is the role of voluntary philanthropy.* But the road today is vastly different and is very bumpy. Our theme as of today and for the future might well be "Is philanthropy an endangered species."

In 1974, Congress passed PL93-641, The National Health Planning and Resources Development Act. This law establishes health priorities and creates the regional planning network (HSA) necessary to see that these goals and objectives are carried out. The net effect of this legislation is to:

1. Exert greater overall control of the health delivery system.
2. Reduce institutional flexibility.
3. Enlarge the bureaucracy.
4. Affect reimbursement.
5. Reduce an institution's ability to plan its own future.

Needless to say, PL93-641 has changed the way hospitals do business drastically. It has also changed the way hospital development will function. Until recently, the development case statement was formed largely by what the administration of the hospital and its board of trustees determined was needed by the institution. In many cases, especially in community hospitals, the Development Committee had frequently identified the source of funding for new programs before the programs were approved for implementation. This was an acceptable way of doing business because most hospitals had little difficulty in gaining the necessary approvals from CHP or other regulatory agencies.

The HSA, however, is different. No longer will hospitals be able to add new services or physical facilities because they are important to the institution's need. All programs now fit within the HSA's Health System Plan and Annual Implementation Plan. Certificate of need forecasting has become a critical part of hospital administration. This leaves development in a difficult spot. It is like having a 747 plan in the air and not having a landing strip.

Some development will have to sit and wait until the hospital planner has gained the necessary endorsement for a particular program before going ahead. Obsolescence is one problem, for example, that cannot wait and requires immediate attention.

By conducting the processes of planning and development in tandem, development not only has input into the planning process but a thorough knowledge of where all projects are at a given time. This enables them to market the development program much more successfully.

We are facing a new kind of health enterprise—one that will fuse public health and the practice of medicine into new systems for the delivery of community and regional comprehensive health care services and facilities. The development of health services is far more important to the welfare of the community than the development of hospitals per se. In terms of fund raising, which depends on community attitudes and traditional community support, this kind of fund raising may be even more challenging.

Financing and reimbursement aside, what will we see in the future in terms of facilities and programs in this new health enterprise? There will be a growing awareness that area-wide health planning could result in a better allocation of resources of comprehensive care based on appropriate levels of health care and a changing role for community hospitals. There will probably be growing self-care units adjacent to the hospital grounds, such things as nonprofit health centers and their will probably be more merging hospitals with lease—management agreements, centralization of management functions. In short, traditional community hospitals will become base lines for other more appropriate levels of care and function as enabling agents to help other health agencies and organizations.

How does all this affect fund raising and the development programs? There must be recognition that new projects and programs requiring capital financing must be based on the total needs of the community, not on what the community thinks it wants or can be "sold." Also, we must recognize that private sector fund raising, while becoming smaller proportionately to other sources of capital financing, will certainly still be important to the life of the hospital, particularly with regard to Deferred Giving and long-range programs. This money will have to be raised to augment Hill-Burton-type programs and state and federal matching grant formulas. The point is that the private fund raising programs, whether they are annual giving programs, Deferred Giving, capital campaigns or specific presentations for foundations, may increasingly be only a fraction of total financing for projects dollar-wise. But, regardless of the sources, this voluntary public-private partnership for health is still called *Development* even though commercial borrowing and financing from "earnings" is still another source.

We all have heard the notion that health care should be devoted to keeping people out of hospitals, not in them. In the coming health care evolution, the development officer will have to fill a role far greater than that of the traditional fund raiser that we have known in the past. A system that recognizes the strength of voluntarism will give America the health care she needs at a price she can afford. One that ignores the *advantages* of voluntary support for health purposes will regress to care of lower and lower quality, and eventually to mediocrity. We value highly the development programs which keep this voluntary strength alive and well. Let us not destroy the very roots of this system by reducing hospital income without controlling costs of hospital labor and supplies. Above all, let us not reduce the incentives for donors to give.

Many development officers have spent considerable time in Washington, D.C., and believe that the Carter Administration's proposed cost containment legislation would have a profound adverse effect on philanthropic giving to hospitals and would seriously erode the capital base of the hospital industry.

It would cause serious deterioration of the nonprofit voluntary hospital structure and provide a major push toward a system in which these hospitals will become essentially federal creatures. By drying up hospital capital funds, the proposed legislation would reduce the quality of patient care, diminish the work and interest of hospital trustees, and curtail the independence of community hospitals. Moreover, requiring hospitals to use up their capital, whether it is depreciation capital or unearmarked philanthropic capital, does nothing to aid cost containment.

As we await the final formulation of a national health insurance plan, (there are five major versions), we take note of the philanthropic language inserted by Congressman Ullman in his bill HR-1: "It is the intent of Congress that appropriate philanthropic support for health care be continued and expanded under the program created by this act, especially in support of experimental, innovative efforts to improve the health care delivery system and access to health care services. Nothing in this act, therefore, is intended nor may be construed to eliminate or *limit* philanthropic support or incentives for such support for health care corporations and health care institutions."

A similar clause preserving private philanthropy was placed in Senator Talmadge's Medicare-Medicaid reform bill that will separate private sector innovative seed money grants from reimbursement formulas.

The New York *Times*, attacked the charitable deduction on its editorial page on September 9th. The charitable deduction is *not* a loophole. It differs from most other deductions and tax preferences in that it is *not economically motivated*. Other deductions inure to the individual taxpayer's benefit. However, the donor would be economically ahead by *not* making a charitable gift because the tax rate is never 100%. Charitable contributions are voluntary and benefit the nation as a whole. Any reduction of current incentives to charitable contributions or a transfer tax on a gift or bequest to charity would, in effect, be an indirect tax on publicly supported charitable organizations.

It is essential for Congress to support the continuation of existing tax incentives for charitable contributions. Any legislate elimination of tax incentives for private philanthropy could damage the whole character of our system because "one of the great strengths of this country has been individual initiative backed up by private contributions."

There are three basic areas of concern: 1) the preservation of the deduction presently allowed charitable contributions; 2) the proposed treatment of gifts of appreciated property; and 3) the prevention of further erosion in tax incentives to charitable giving.

There are thousands of individuals, trustees and auxilians who are willing to show leadership, to take the initiative in everything from supporting our local hospitals to funding experimental research and they feel that their efforts count. This broad voluntary participation gives remarkable vitality to what John D. Rockefeller III called "the third sector."

In development it is important for us to nourish that third sector both financially and spiritually.

People tend to put their hearts where their money and time are voluntarily given—it brings out the energy and creativity in people when they invest a part of themselves in a project. There are an estimated 150 thousand trustees and 350 thousand auxilians involved with hospitals. All told, counting volunteers, about 5-million people are involved.

The cost of this vast network of concerned individuals is absolutely zero and this is the essence of voluntarism. The replacement cost of this national voluntary service would be untold billions. The impact in the budget and tax structure would be enormous. The truth is that only when one has the right balance of money and confident leadership are things done well. It is axiomatic that the philanthropic or third sector is of equal importance with government and business.

We are also concerned about the Federal $2.5-billion and $40-million NY State proposed *limit* on capital expenditures by hospitals from their *own* philanthropic funds because it simply may not be enough money to go around to cover our needs. Why should there be a $2.5-billion limit for capital expenditures when the private sector gave almost *$4-billion in 1977 for hospitals alone.*

There are also further complications. Under present tax law, a donor must donate money for a piece of equipment within a specific time period to gain the best tax advantage and this may be out of synchronization with the Carter bill. We are also concerned that philanthropic funds not be used to subsidize Blue Cross or the government rather than be used for its intended charitable purpose such as patient care not supported by Blue Cross or government monies. Those of us closest to the development scene are concerned that any National Health Insurance scheme may give donors the false impression that hospitals and health care institutions no longer need their support because it is provided by the Government. They might, therefore, switch their philanthropy away from hospitals.

Philanthropic giving is dependent on a high degree of credibility. Any tampering with this vital fact will numb the delicate instinct for giving. We must not turn off this source for new equipment, privately sponsored research, and facilities as long as we do not seem to add to our bed capacities.

More than 2 million people in this country have assets of more than half a million dollars each. There is thus a great untapped potential for meeting our ongoing and capital needs from those who will give appreciated securities or cash contributions. The donor's *designated* wish must be respected.

It would probably be illegal and perhaps even unconstitutional for Congress and the regulators to break contracts existing between hospitals and donors by diverting this designated money for general revenue.

Fortunately, representative Tim Lee Carter has introduced an amendment in the Cost Containment Legislation HR 6575 to give us this protection and also protection from invasion by the Government of our unrestricted funds restricted by the hospital's governing body for nonoperating purposes.

Therefore, significant legislative and regulatory matters affect hospital philanthropy. The impact is also on each and every development officer, adding a new and urgent dimension to the role. This dimension concerns first the responsibility of being informed about these significant legislative and regulatory matters, and second, informing the hospital leadership. In effect, being a town crier.

Chief executive officers, the controllers, and hospital planners, to name a few specialists, are already swamped. In addition to carrying out their daily duties, they are at the same time watching very carefully the Carter administration's "efforts" to reinstitute some form of price control on hospitals throughout the country which could lead to a national health act without voluntarism!

Thus, the new dimension surfacing for trustees and directors of development is critical. It is imperative that each development officer become an informed reporter to reach the institutions's trustees, medical staff, management team, and donors about the threats to philanthropy. Again, a gloomy prognosticator might ask, "Is philanthropy an endangered species?"

Development officers justifiably pride themselves on their skill in preparing case statements of need and writing proposals that produce dollar results in the form of gifts. That skill needs to be called upon *now* to produce forceful and persuasive statements about the current legislation problem. Our publics not only must be informed but also moved to take action.

There is nothing either illegal or immoral about this latter course thanks to HR 13500 and the Filer Commission; it is a known and proven fact that legislators at all levels will respond when they hear from their constituents.

Finally, we must continue to seek the funds. Our cause is honorable, our needs continue, and, since we still live in a pluralistic society, we should not have hesitancy in asking people and organizations to continue to give.

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Coping with Hospital Strikes*

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From July 7 through 17, 1976, District 1199, National Union of Hospital and Health Care Employees, staged a strike that affected all member institutions of the New York City League of Voluntary Hospitals and Homes. The walkout, unlike the one staged in 1973 (November 5 through 12), was one with which the hospitals were prepared to cope.

Contingency plans were implemented once a federal law preempted the National Labor Relations Act, which sought to outlaw hospital strikes. These measures included:

1. Stockpiling of essential supplies
2. Categorizing patients into three classes:
   a. able to be sent home
   b. probably could be sent home
   c. definitely required care
3. Consolidating patients into fewer wards
4. Assigning all functions which normally were performed by the striking workers (virtually all employees except registered nurses and physicians) to supervisors, professionals and volunteers remaining on the job.§

In addition, the Board of Health authorized the City's Health Commissioner to declare a health emergency, if necessary, to enable delivery and sanitation trucks to pass through the picket lines. This would allow hospital services to continue with minimal interference.

The purpose of this study is to determine:

1. The actual gross and net dollar losses for an institution as a result of the strike.
2. What effect, if any, the first strike had on hospital management in preparing contingency measures to minimize the negative economic effect and disruption of patient care.

Selected for analysis was one of New York City's largest nonprofit voluntary hospitals with over 1000 beds. In an attempt to make a more meaningful comparative analysis, the 1976 strike, which lasted eleven days, was converted into an eight-day base to conform with the eight-day 1973 walkout. In addition, pay scales and per diem reimbursement rates were made comparable.

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* This study was authorized by The Mount Sinai Medical Center, New York, N.Y. 10029.

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§ Hospitals Girding for Strike Today, *The New York Times*, July 7, 1976, page 1.

Normal Operating Costs Saved

During the strike the hospitals "saved" money by not paying salaries and employee benefits to the striking workers. This amounted to savings in the 1976 strike of \$750,000 in salaries and \$166,000 in fringe benefits not paid out to striking 1199 employees. Comparable figures for the 1973 strike were \$400,000 and \$70,000, respectively. Calculating the average *daily* savings for the strikes we find \$83,000 daily savings in 1976:

$$\frac{\$750{,}000 \text{ salary} + \$166{,}000 \text{ fringe savings}}{11 \text{ pay days lost}} = \$83{,}000$$

as compared to \$59,000 in 1973:

$$\frac{\$400{,}000 \text{ salary} + \$70{,}000 \text{ fringe savings}}{8 \text{ pay days lost}} = \$59{,}000$$

The percentage difference in the average daily savings can be attributed to a 22% salary and benefit package increase (accounting for 75% of the difference in savings between the two strikes), as well as an increase in the number of 1199 workers.

Patient Revenues Lost

The major negative effect on the hospitals during the strike was the loss of patient revenues that would have been accrued under normal circumstances. Losses were felt in the Emergency Room (ER), Outpatient Department (OPD), as well as in Inpatient Medical/Surgical (Med/Surg) Units. In order to determine the loss of patient visits and days attributed to the strike, the number of visits in the respective strike months (November 1973 and July 1976) were compared to the average number of visits in the 3 months prior to the strike and to the 3 months after the strike, to control for possible seasonal effects. Furthermore, in an effort to eliminate possible time trend effects, similar analysis was performed for the two years preceding each strike as measured by the percent difference for 3 months prior to and 3 months after the strike month between 1971 and 1976. The results (Table I) reveal several interesting developments.

1. The ER operated more effectively during the second strike as compared to the first one. This is seen by examination of the percentages for the strike periods in 1973 and 1976. The difference, in order of magnitude and sign, indicates much less of a decline in ER visits in the 1976 strike. The difference is statistically significant (see discussion below).
2. The OPD provided fewer services during the second strike. This, too, may be seen by the percentages for the 1973 and 1976 strikes as noted in (1) above.
3. The Med/Surg Units operated approximately at the same level during the two strikes. Once again, this may be seen from the percentages in Table I.
4. The ER, OPD, and Med/Surg Units were generally less utilized during

TABLE I

*Hospital Days/Visits and Percent Change during Strike Month Compared with Three Month Averages prior to and after Strike**

	1971	1972	1973 strike	1974	1975	1976 strike
			Emergency Room			
3 months prior to strike month	−2482	−359	−1067	+97	+827	+21
	(−33.2)**	(−7.0)	(−21.7)	(+2.0)	(+17.3)	(+.5)
3 months after strike month	+60	+134	−688	−655	+279	−550
	(+1.2)	(+2.9)	(−15.1)	(−11.7)	(+5.2)	(−10.9)
			OPD			
3 months prior to strike month	+5675	+839	−3737	−634	−1828	−9788
	(+25.7)	(+4.7)	(−21.4)	(−3.4)	(−8.5)	(−45.7)
3 months after strike month	+213	+908	−3895	+397	−1713	−8611
	(+1.2)	(+5.2)	(−22.1)	(+2.3)	(−8.4)	(−42.5)
			Med/Surg			
3 months prior to strike month	−17	+67	−2917	+859	−142	−2373
	(−.1)	(+.3)	(−11.6)	(+3.4)	(−.5)	(−8.5)
3 months after strike month	−274	+319	−2418	+748	+608	−1507
	(−1.1)	(+1.2)	(−9.8)	(+3.0)	(+2.4)	(−9.4)

* (−) indicates a percent decrease. **This figure for 1971 is nonrepresentative because of the reorganization of the ER affecting total visits.

the respective strike month compared to the pre and post three-month periods, with the possible exception of the ER. During July 1976, the ER was utilized as much as during the prior three-month period.

A major shift in priorities seems to have taken place in the second strike. Whereas in the first strike an attempt was made to operate all services in the hospital, the 1976 strike emphasized emergency care at the expense of preventive and acute self-limiting nonemergency care. Thus, there were virtually no differences in the 1973 percentage change of utilization rates in these areas. Furthermore, the hypothesis that a decrease in outpatient utilization would result in a concomitant increase in ER utilization was tested. The decrease in outpatient utilization can be calculated as the difference between percent difference for OPD visits during 1973 and 1976 strike periods (Table I). Similarly, the increase in ER utilization can be calculated as the difference between the ER percent differences. The discrepancy between these two differences was tested by a Student "t" test with 2 degrees of freedom. While strongly suggestive, the difference fell just short of statistical significance ($.05 < p < .1$).

In addition, Student "t" tests were performed on actual data comparing the index, or strike month statistics, with the average of (1) the three-months prior to and (2) the three-months post the index month in question, for all years between 1971 and 1976. "Strike months" refers to November for the years 1971–1973 and July for the years 1974–1976. These tests were performed for each of the index strike months, independently. The results indicate that for nonstrike years, the null hypothesis was sustained in each case. However, for the strike years, the hypothesis was rejected for the OPD and Med/Surg Units in the 1976 strike, as well as for the ER and Med/Surg Units in the 1973 strike.

This confirms the belief that there was a priority change from the OPD to the ER in the 1976 strike.

	1973 Strike	*1976 Strike*
ER	Significant ($p < .05$)	Not Significant
OPD	Not Significant	Significant ($p < .01$)
Med/Surg	Significant ($p < .05$)	Significant ($p < .05$)

In order to calculate the actual number of days or visits lost due to the strike, for the ER, OPD, and Med/Surg Units, the following computation is made:

1. the combined average of the number of days/visits for the 3 months prior and 3 months after the strike is calculated
2. the actual number of days/visits that occurred during the strike month is subtracted from the calculated average

For example, the 1976 Medical/Surgical Units lost 2433.0 days (Table II).

$$\frac{26{,}485 \text{ (3 mo. avg. prior)} + 26{,}605 \text{ (3 mo. avg. after)}}{2} - 24{,}112 \text{ (\# of visits in strike mo.)} = 2{,}433 \text{ days}$$

Table II illustrates the estimated number of days/visits lost for each service.

TABLE II

Estimated Number of Days/Visits Lost per Service

Service	1973	1976
Emergency Room Visits	877.5	264.0
Outpatient Department Visits	3816.0	9199.5
Medical Surgical Days	2667.5	2433.0

In order to quantify the loss of revenue, each service is broken down in Table III, according to the percent of visits for each reimbursement category.

The estimated total gross dollars lost in the 1976 strike as a result of a decrease in the number of visits made to the hospital was $1,001,001.22. This represents a 70.0% increase over the 1973 figure of $588,935.34:

$$\frac{\text{(\$412,065.88) additional \$ lost in 1976}}{\text{(\$588,935.34) 1973 total \$ lost}} \times 100 = \text{\% additional loss} = 70.0\%$$

One may gain additional insight into the effects of the strike if the difference in the length of the strike and the difference in the reimbursement rates are appropriately adjusted.

Length of the Strike

The 1973 strike lasted eight days, (Monday, November 5 through Monday, November 12), whereas the 1976 strike lasted 11 days (Wednesday, July 7 through Saturday, July 17). Thus, the 1976 figures were reconstructed to

TABLE III

Total Dollars Lost per Reimbursement Category (i.e.: Medicaid, Medicare, Self-Pay and Blue Cross, as recorded by the hospital under study) for the 1973 & 1976 Strikes

Reimbursement category	% of Visits in each category	×	Visits lost in month	=	Visits lost per category	×	Rate per category	=	$ Lost per category
			Emergency Room						
November 1973									
Medicare	7.6		877.5		66.69		$14.90		$993.68
Medicaid	38.7				339.59		$19.65		$6672.94
Self-pay/others	53.7				471.21		$5.80		$2733.91
	100.0				877.49				$10399.63
July 1976									
Medicare	9.4		264.0		24.81		$29.51		$732.14
Medicaid	35.2				92.92		$40.25		$3704.03
Self-pay/others	55.4				146.25		$8.69		$1270.91
	100.0				263.98				$5707.08
			Outpatient Department						
November 1973									
Medicare	8.7		3816.0		331.99		$18.20		$6042.21
Medicaid	44.8				1709.56		$49.94		$85,375.42
Self-pay/others	46.5				1774.44		$5.75		$10,203.03
	100.0				3815.99				$101,620.00
July 1976									
Medicare	11.7		9199.5		1076.34		$29.47		$31,719.73
Medicaid	42.6				3918.98		$67.72		$265,393.32
Self-pay/others	45.7				4204.17		$9.24		$38,846.53
	100.0				9199.49				$335,959.58
			Medical/Surgical						
November 1973									
Medicare	32.0		2667.5		853.60		$172.50		$147,246.00
Medicaid	18.9				504.60		$172.80		$87,117.12
Blue Cross	32.7				872.27		$170.00		$148,285.90
Self-pay/others	16.4				437.47		$215.48		$94,266.03
	100.0				2667.49				$476,915.05
July 1976									
Medicare	38.6		2433.0		939.13		$253.00		$237,599.89
Medicaid	13.3				323.58		$253.00		$81,865.74
Blue Cross	33.2				807.75		$278.00		$224,554.50
Self-pay/others	14.9				362.51		$318.10		$115,314.43
	100.0				2432.97				$659,334.56

Total dollars lost in 1976 = $1,001,001.22
Total dollars lost in 1973 = $588,935.34

Additional dollars lost in 1976 = $412,065.88

reflect 8/11 of the dollars lost for the ER and Med/Surg Units. The actual effect of the strike on the OPD, however, was only 6 days for 1973 and 8 days for 1976 because these clinics do not operate on the weekends. Therefore, the 1976 OPD figures were reconstructed by a factor of 6/8. In addition, the 1976 per diem rates were converted into the 1973 rates to assure comparability (Table IV).

Once these figures have been adjusted, to allow comparable analysis, we find that the total dollar loss to the hospital due to fewer patient visits and patient days during the strike amounts to $496,973.59 in the 1976 strike. This reflects a 15.6% decrease from the 1973 strike loss of $588,935,43.

A comparison of the total dollars and days/visits lost in each category, shown in Table IV, once again illustrates the shift in emphasis away from the OPD to ER and Med/Surg Units during the 1976 strike.

Strike-Related Expenses

Overtime: During the strike, efforts were made to operate the hospital effectively as possible. Thus, employees not on strike were asked to fill the void by working additional hours. Two groups of personnel were utilized (1) administrative and (2) other nonbargaining unit employees. The dollar amounts paid to these employees for the two strikes are quite interesting (Table V).

The additional salaries and fringe benefits paid out to non-bargaining unit employees in 1976 were 20.5% less than that paid out in the 1973 strike. Converting these figures to reflect the 1973 strike (comparable length of strike and comparable pay scales) we find that there was a 45.8% decrease in additional salary costs. This is determined by:

1. Calculating the average cost per day for additional salaries.
2. Converting the 1976 pay scale to the 1973 base scale.
3. Multiplying the average cost per day by the adjusted number of strike days (8 days).

The average additional cost for the 1973 strike was $96,000 ($770,000 ÷ 8 additional days) as compared to $56,000 for the 1976 strike, ($612,000 ÷ 11

TABLE IV

1973 and "Adjusted" 1976 Dollars and Days/Visits Lost

	1973 dollars	1973 days/visits	1976 adjusted dollars	1976 adjusted days/visits
Emergency Room	$10,399.63	878	$2,213.61	192
Outpatient Department	$101,620.66	3816	$179,606.97	6900
Medical/Surgical Units	$476,915.05	2268	$315,153.01	1769
Total $ Lost for the 3 Services	$588,935.34		$496,973.59	

TABLE V

Comparison of Additional Salaries and Benefits Paid in the 1973 & 1976 Strikes

Categories	1973	1976
Additional Salaries paid to Administrative Staff	$320,000	$290,000
Additional Salaries paid to other Nonbargaining Unit Employees	$400,000	$305,000
Additional Non-Bargaining Unit Fringe Benefits	$50,000	$17,000
Total Additional Salaries and Benefits	$770,000	$612,000

additional pay days). After adjusting the pay scales, the average cost per day would have been $46,000.

The difference in the dollar amounts paid can be attributed to policy changes made during the second strike. During the first strike, all nonbargaining unit employees—administrative and non-adminsitrative personnel—were paid time and a half. Only the non-administrative personnel were so reimbursed during the second strike. Administrative personnel were reimbursed straight time.

The experience gained from the first strike can also be seen when one looks at other strike related expenses incurred during the first strike but avoided during the second one. These additional expenses include food costs, outside security guard, and petty cash for supplies and equipment*

Food Costs: During the 1973 strike, the hospital under review did not charge its employees for food consumed in the cafeteria. Thus, $25,000 of revenue which normally would have accrued, was lost. In addition, an extra $25,000 was spent in buying frozen foods for its employees who were served on paper goods and plastic tableware instead of regular dishes and tableware. In the 1976 strike, the cafeteria operated as usual with employees paying for their meals.

Security Expenses: In an attempt to augment the security in the hospital, additional security guards were hired from the contract security service during the 1973 strike. An additional $55,000 had to be allocated for this service in order to maintain some sense of order in the hospital. In 1976, the hospital arranged special contingency measures in the event of a strike and thus no additional monies were spent for security. These measures included cooperation with the police department which beefed up the number of officers guarding the institution.

Supplies and Equipment: Estimated supplies and equipment expenditures, unlike those for security and food, were higher in the 1976 strike—$30,000 in 1976 compared to $10,000 in 1973. The bulk of this money was spent primarily to buy assorted disposables for the Med/Surg Units, the area on which the hospital placed its greatest emphasis. (A fraction of the increase in expenditures is attributed to inflation.)

Constructing a comparable balance sheet of the two strikes, we find that although the 1976 strike lasted longer, and although the hospital stood to lose more because of higher per diem rates, there was a 27.6% decrease in the cost of the 1976 strike. Furthermore, once the strike is adjusted for duration and dollar changes in salaries and per diem rates, we see a 65% decrease in costs. This is illustrated in Table VI.

Impact of Strike

A comparison of the *gross* cost of the strike reveals that in 1976 the hospital incurred $277,000 less in costs than in 1973, even though the 1976 strike lasted for three more days. The overall *net* cost, however, was higher for the 1976 strike. This was the result of a policy decision made by New York State not to

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* For a more detailed description of strike related expenses see: Paul E. Brody & Jordan London "How Costly is a Strike?" *Hospitals, JAHA*, September 16, 1975 pp. 53–56.

TABLE VI

Comparison of Total Costs and Adjusted Costs of the 11-Day (July 7–17, 1976) Strike and the 8-Day (November 5–12, 1973) Strike

Expenses	1973	1976	1976 adjusted
Loss of income due to loss of Inpatient days	$477,000	$659,000	$315,000
Loss of income due to loss of Outpatient Department visits	$102,000	$336,000	$180,000
Loss of income due to loss of Emergency Room Visits	$10,000	$6,000	$2,000
Additional salaries paid to Administrative Staff	$320,000	$290,000	$173,000
Additional salaries paid to other Nonbargaining Employees	$400,000	$305,000	$182,000
Additional Nonbargaining Employees Fringe Benefits	$50,000	$17,000	$10,000
Additional Security	$55,000	–0–	–0–
Additional Food Costs	$25,000	–0–	–0–
Loss of revenue from Cafeteria	$25,000	–0–	–0–
Additional Supplies & Equipment	$10,000	$30,000	$30,000*
Total Expenses	$1,474,000	$1,643,000	$892,000
Savings			
Salaries not paid to 1199 Employees	$400,000	$750,000	$447,000
Savings on 1199 Union Employee Benefits	$70,000	$166,000	$99,000
Total Savings	$470,000	$916,000	$546,000
Gross Cost of Strike	$1,004,000	$727,000	$346,000
% Change in Cost of Strike		27.6%	65.5%

* No adjustments were made for additional supplies and equipment.

TABLE VII

Amount Reimbursed By Third Parties

Third parties	Dollar amount reimbursed	
	1973	1976
Blue Cross Appeal	$330,000	–0–
Medicare Appeal	$365,000	$220,000
Medicaid Appeal	$285,000	–0–
Total	$980,000	$220,000

adjust the reimbursement rates. Whereas, in 1973 rate adjustments were made to offset some of the hospital's unforeseen strike losses, the State froze the 1976 reimbursement rate (Table VII).

This policy had an obvious devastating effect on the hospital. The gross cost of the strikes were $1,004,000 for 1973 and $727,000 for 1976 (see Table VI). Subtracting the dollar amount of reimbursement from the gross cost of the strike, we find that in 1973 the hospital lost only $24,000 compared to $507,000 in 1976.

	1973	*1976*
Gross Cost of Strike	$1,004,000	$727,000
Reimbursement by Third Parties	$980,000	$220,000
Net Cost of Strike	$24,000	$507,000

Summary

Less than three years after New York City experienced its first hospital strike, a second walkout occurred in July, 1976. However, unlike the first strike where the hospitals were caught off guard, hospital management prepared contingency measures in an effort to minimize disruption to patient care and to reduce the negative economic effect.

Based on detailed analysis of a major voluntary hospital, the contingency measures seemed to have had a positive effect. (Caution must be exercised not to draw inferences for the entire hospital system for no claim is made that this is a wholly representative hospital.)

1. Focus of attention turned to the treatment of patients most in need of medical care (Emergency Room and Med/Surg Units), at the expense of preventive and acute self-limiting care. Thus, one can see (Table I) a significant dropoff in the number of outpatient visits during the strike month when compared to the three months prior to and three months after the strike. On the other hand, the Emergency Room and the Medical/Surgical Units operated almost at capacity.

2. Strike-related expenses (additional security, additional food costs, and loss of revenue from cafeteria services) were totally eliminated during the second strike.

3. Overtime expenses were drastically reduced by instituting new procedures whereby administrative personnel were reimbursed straight time in place of time and a half.

The overall monetary effect was a 27.6% decrease in the *gross* cost of the 1976 strike as compared to the 1973 strike. This is a remarkable achievement in view of the fact that the 1976 strike lasted 3 more days than the 1973 strike. The net dollar effect, however, was in reverse; the strike in 1976 cost $483,000 more than the 1973 strike. This was the result of the State's decision to freeze reimbursement fees.

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NEUROLOGIC—NEUROSURGICAL NOTES

ALLAN E. RUBENSTEIN, M.D. AND MARTIN H. SAVITZ, M.D., COEDITORS

Peripheral Catecholamine Depletion in Amyloid Autonomic Neuropathy

Submitted by

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Abstract

The cause of orthostatic hypotension in a patient with amyloidosis was investigated. Intravenous infusion of dilute norepinephrine produced a marked hypersensitive response with concomitant peripheral vasoconstriction. Muscle and rectal mucosa biopsy examined by histofluorescent technique revealed the peripheral adrenergic nerve endings to be depleted of catecholamines. Extensive amyloid infiltration of the peripheral autonomic nervous system was present at autopsy. Orthostatic hypotension in amyloidosis occurs as a result of a diffuse autonomic neuropathy and is not caused by amyloid infiltration of peripheral resistance blood vessels.

The clinical manifestations of amyloidosis not infrequently include symptoms of autonomic nervous system dysfunction such as orthostatic hypotension (OH), chronic diarrhea, dyshidrosis, impotence, and bladder disturbance (3, 6, 13, 15). Often these problems appear concomitantly with a peripheral neuropathy, though on occasion they may precede any clinical evidence for peripheral sensory or motor nerve dysfunction. Orthostatic hypotension may be the presenting and only initial complaint, and of such severity that the patient may be labeled as idiopathic orthostatic hypotension (IOH) unless suspected of and investigated for amyloid disease (12, 17).

There has been some confusion over the etiology of OH in amyloidosis. Mallory et al (14) assumed that the OH in a patient with primary amyloidosis and nephrotic syndrome was due to hypovolemia. Wagner in 1959 discussed a case of primary amyloidosis in which intravenous norepinephrine and vasopressin did not improve the OH (21). He concluded that direct amyloid infiltration of peripheral resistance blood vessels was responsible. This point of view has persisted and has been reemphasized in a recent review on OH (9). Several authors have found amyloid infiltration in autonomic ganglia at

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autopsy and concluded that this was the etiology of the OH in their cases (3, 6, 15). However, it is not yet clear that amyloid deposition in the peripheral nervous system is in itself wholly responsible for peripheral nerve dysfunction. Coimbra and Andrade have presented evidence that in hereditary amyloidosis, nerve degeneration precedes amyloid fibril deposition in nerves (4). Trotter et al (20) have postulated that a circulating neurotoxic substance is produced in amyloidosis. Sural nerve biopsies in several studies have shown loss of unmyelinated and myelinated fibers (10, 19, 20). All the patients studied had sensorimotor neuropathies, and, therefore, it is not possible to determine if the unmyelinated fiber loss was a result of involvement of sensory "C" fibers or postganglionic autonomic fibers.

A variety of physiologic, pharmacologic, and histochemical techniques are available to determine whether or not OH is neurogenic and, if so, whether the site of the autonomic dysfunction is central or peripheral (18). We wish to describe a case of primary amyloidosis presenting as OH in which several of these techniques were utilized to document peripheral autonomic dysfunction as the cause of the OH.

Case Report

A 55-year-old man was admitted to The Mount Sinai Hospital in January 1977, for evaluation of severe dizziness and syncope on standing. The patient had been mildly hypertensive and in 1974 was started on methyl-dopa and a diuretic. In November 1975, the patient developed dizziness on standing and orthostatic changes in the blood pressure were noted. His antihypertensives were discontinued, with a mild but transient improvement in his postural hypotension. During the next six months his symptoms worsened and he had several episodes of loss of consciousness on standing. He then developed chronic diarrhea and lost 30 pounds. There was no history of diabetes, alcohol ingestion, or exposure to industrial toxins. The family history was negative for neurologic disease.

The patient was admitted to Long Island Jewish Hospital where neurologic examination was reportedly normal. Routine studies of the blood and urine were normal. A three-hour glucose tolerance test was normal. Analysis of the urine for porphobilinogen, Bence-Jones protein, and heavy metals was negative. Urinary catecholamine metabolites were normal. An intravenous pyelogram and a barium enema were normal. Skull x-ray, EEG, and brain scan were normal. A systolic ejection murmur was heard at the left sternal border that became louder on standing. An EKG showed sinus rhythm with inverted T waves in leads 2, 3, AVF, V5 and V6; poor R wave progression in V1-V2. An echocardiogram and phonocardiogram were interpreted as consistent with idiopathic hypertrophic subaortic stenosis (IHSS). The patient was diagnosed as having idiopathic orthostatic hypotension (IOH) and IHSS. He was started on propranolol for IHSS and was treated for IOH with a monoamine oxidase (MAO) inhibitor and tyramine-containing foods.

His postural symptoms persisted and the patient was subsequently started on fludrocortisone acetate, 0.1 mg orally twice a day, with only a mild and transient improvement. He subsequently developed impotence and loss of nocturnal erections without change in libido, followed by progressive numbness and weakness of his legs.

On examination the blood pressure supine was 140/75 mm Hg; standing it was unobtainable. Pulse, respiration, and temperature were normal. General physical examination was normal except for a loud systolic murmur at the left sternal border and mild ankle edema. The tongue was normal in size and there was no organomegaly. Neurologic examination revealed a normal mental status and normal cranial nerve function. Deep tendon reflexes were 1+ and symmetrical in the arms: absent in the legs. There were no pathological reflexes. There was bilateral leg weakness, distal greater than proximal, and the patient walked with an unsteady, slapping gait indicative of bilateral foot drop. Muscle tone was normal; there was no muscle tenderness, fasciculation, or atrophy. Sensory examination showed a symmetrical stocking distribution loss to pain, temperature, light touch, vibratory and position sensation. There was no dysmetria.

Laboratory findings: Hemoglobin was 13.7 gm %; hematocrit 41.8%. White blood cell count, differential, platelet count, reticulocyte count, and ESR were all normal. Serum glucose, BUN and routine electrolytes were normal. A five-hour glucose tolerance test was normal. Serum calcium, phosphorus, and liver function tests were normal. Serum cholesterol was 152 mg % (normal, 160–330 mg %); total protein, 5.4 gm % (normal, 6.0–8.3 gm %); albumin, 3.2 gm % (normal 3.5–4.9 gm %). Urinalysis was normal except for 1+ proteinuria. Twenty-four hour urine protein was 0.5 gm. Analysis of the urine for Bence-Jones protein was negative. Serum immunoelectrophoresis showed mild hypogammaglobulinemia. Bone marrow was normal. Serum folate was normal; serum B_{12} was 113 pg/ml (normal 200–900 pg/ml). A Schilling test, D-xylose absorption test, and 24-hour fecal fat assay were all indicative of malabsorption. An upper gastrointestinal series with small bowel follow-through showed thickened edematous folds in the duodenum. Barium enema and an intravenous pyelogram were normal. An echocardiogram was interpreted as consistent with IHSS. An electroencephalogram was normal. Nerve conduction velocities and needle electromyography were indicative of a diffuse polyneuropathy. A rectal biopsy showed extensive deposition of amyloid. A gastrocnemius muscle biopsy showed small angulated fibers and type grouping consistent with denervation. Crystal violet and congo red stains showed amyloid deposition in connective tissue.

Autonomic studies: Tilt table testing showed a drop in blood pressure from 145/80 mm Hg to 55/45 mm Hg with no increase in pulse on 90 degree tilt. An attempt at Valsalva maneuver while supine resulted in a syncopal episode lasting for 10 seconds. There was no increase in pulse or B.P. to 60 seconds of an ice-water stimulus. Digital blood flow, measured with a finger plethysmograph coupler on a Beckman R511 dynograph recorder, showed no vasoconstriction during the cold pressor test. Intradermal injection of .1 cc Histamine 1/1000 solution produced a normal wheal with an absent flare response. Blood pressure, pulse, and digital blood flow were continuously monitored during intravenous injection of dilute norepinephrine (NE) in concentrations of .5 to 3.0 μgm/min, a range below the minimum infusion rate required to raise blood pressure in a normal adult (23). There was a marked hypersensitive response to infused NE (Fig. 1); the blood pressure increased to 235/105 mm Hg at an infusion rate of 3.0 μgm/min, at which time the infusion was discontinued. The maximum percentage increase in systolic blood pressure was 1.1 per ng NE/kg/min. The maximum percentage increase in systolic blood pressure in an age-matched normal control was .09 per ng NE/kg/min. Pulse rate remained constant during the infusion.

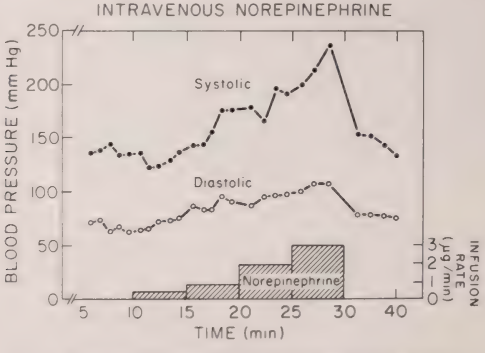


FIG. 1. Hypersensitive response to dilute intravenous norepinephrine.

Digital blood flow decreased to 50% resting blood flow during the infusion. Muscle and rectal biopsy specimens were stained for catecholamine histofluorescence of perivascular adrenergic nerve endings using the Falck-Hillarp technique (5). A muscle specimen not treated with formaldehyde vapor was used to determine the specificity of fluorescence. There was complete absence

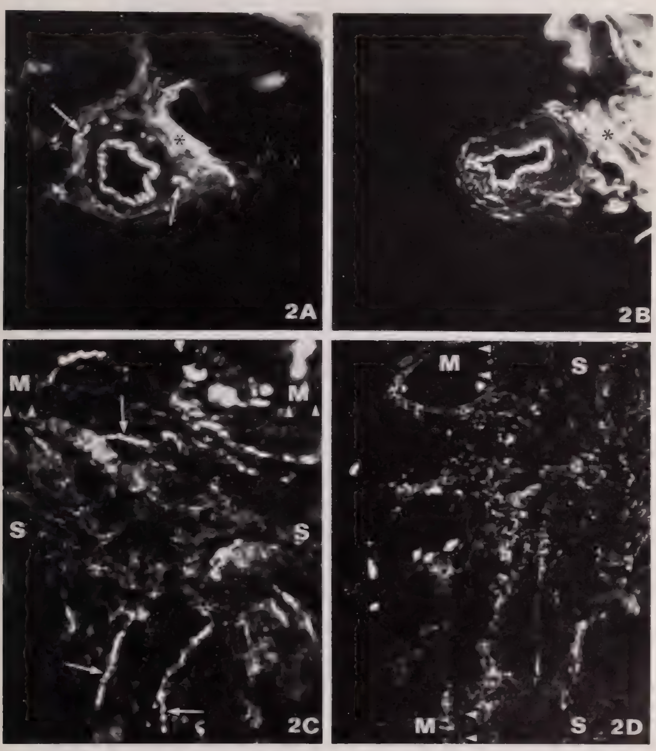
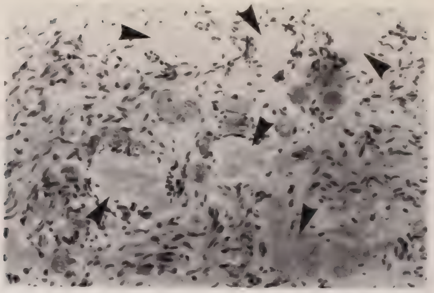


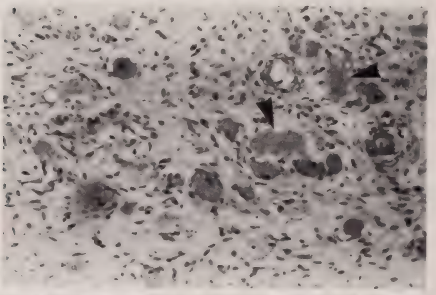
FIG. 2A. Fluorescence photomicrograph of a blood vessel from a biopsy from a control subject. The arrows point to adrenergic nerve terminals which give green formaldehyde induced fluorescence specific for catecholamines. There is some nonspecific fluorescence in the surrounding tissue (asterisk). The internal elastic membrane shows orange autofluorescence (x 160).

FIG. 2B. Blood vessel from a muscle biopsy from a patient with amyloidosis. There is a complete lack of specific catecholamine fluorescence. Nonspecific fluorescence is present in surrounding tissues (asterisk). The internal elastic membrane of the blood vessel shows orange autofluorescence (x 160).

FIG. 2C. Fluorescence photomicrograph from the rectal biopsy of a control subject. Several adrenergic nerve fibers with distinct varicosities (arrows) are present in the submucosa (S). Arrowheads point towards the mucosa (M) (x 160).

FIG. 2D. Photomicrograph showing complete absence of sympathetic innervation in the submucosa (S) of the patient with amyloidosis. Arrowheads point toward the mucosa (M) (x 160).





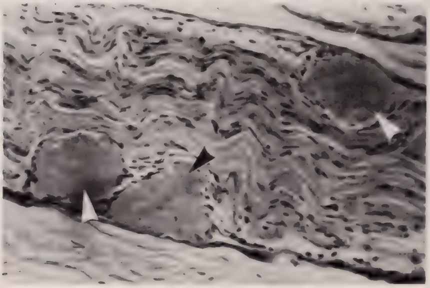


FIG. 3A Top. Photomicrograph of a section from thoracic sympathetic ganglion stained with hematoxylin-eosin. Arrows point to masses of amyloid infiltration x 110.

FIG. 3B Middle. Sections from celiac ganglion. Congo red stain. Amyloid infiltration indicated by the arrows x 116.

FIG. 3C Lower. Longitudinal sections through the sciatic nerve. Three large masses of amyloid are present (arrows). Congo red stain x 110.

of peripheral catecholamine stores in all muscle sections examined (Fig. 2). A specimen of muscle was incubated with α-methyl NE and subsequently stained for histofluorescence. There was no catecholamine uptake into adrenergic nerve endings. Similarly there was no catecholamine histofluorescence in adrenergic nerve endings in the rectal biopsy (Fig. 2). The patient continued to have severe postural hypotension despite treatment with MAO inhibitors and ergotamine tartrate. He was subsequently discharged and died suddenly a month later following a hypotensive episode.

Autopsy findings: On autopsy there was amyloid deposition in the liver, spleen, pancreas, and tongue. Minimal amyloid deposition was present in the submucosa and lamina propria of the stomach, small intestine, and colon. Amyloid infiltration of the heart was present in addition to biventricular hypertrophy. Random sections of bone marrow showed a mild but definite plasmacytosis with only occasional immature forms. No amyloid was seen in the marrow. There was no amyloid deposition in the brain and spinal cord. Extensive amyloid deposits were seen in all peripheral nerves examined, in both sympathetic chains, in all dorsal root ganglia, the celiac ganglia, and in the intrinsic enteric nerve supply of the small and large intestines (Fig. 3).

Discussion

The diagnosis of IHSS made premortem was not supported at autopsy. The abnormalities leading to that diagnosis were explained by amyloid infiltration of the heart. IHSS or amyloid infiltration in a similar distribution could have worsened the patient's OH, though it is improbable that it was the primary cause of the OH in our case.

The lack of evidence premortem for a plasma cell dyscrasia would place this patient in the category of nonhereditary primary amyloidosis. The finding of a mild plasmacytosis in the marrow at autopsy is consistent with the view that all cases of primary amyloidosis represent a minor degree of plasma cell dyscrasia (20).

The etiology of the chronic diarrhea commonly seen in amyloidosis has never been settled. The extensive amyloid infiltration of the neural innervation of the digestive tract found at autopsy combined with the scanty amount of amyloid found in the intestinal tract itself suggest that autonomic dysfunction is responsible. Several reports have found a similar pattern of amyloid involvement in the intestinal tract (2, 6). Catecholamine depletion of intrinsic adrenergic nerves in the rectal mucosa has not been previously reported in amyloidosis and is further evidence of an autonomic etiology to the diarrhea. Penttilla et al (16) found normal catecholamine content in 5 rectal biopsies from patients with amyloidosis, but none of their patients had any clinical autonomic dysfunction.

The lack of response to an ice-water stimulus is evidence for interruption in the efferent sympathetic pathway, as there was no impairment of temperature sensation in the immersed hand. The marked hypersensitive response to infused dilute NE is indicative of denervation hypersensitivity of receptors for peripheral adrenergic nerve endings (23). That the peripheral resistance vessels were intact despite some perivascular amyloid deposition is indicated by the vasoconstriction demonstrated by digital blood flow during the NE infusion. These data do not support the generally accepted concept that OH in amyloidosis is an example of effector organ failure. The lack of reflex bradycardia as the blood pressure increased during the NE infusion is evidence of additional failure of the baroreceptor mechanism and/or its connections. Baroreceptor reflex dysfunction is common in other diffuse autonomic neuropathies (1).

The lack of catecholamine histofluorescence on muscle biopsy and the failure of incubated adrenergic nerve endings to take up NE are proof of peripheral catecholamine depletion and indicate postganglionic adrenergic fiber dysfunction. Kontos et al (11) reported similar catecholamine depletion in 4 patients with IOH and Yahr (22) has reported catecholamine depletion with failure of NE uptake in 1 case of familial dysautonomia. Both IOH and familial dysautonomia are examples of OH caused by postganglionic adrenergic nerve dysfunction. Goodall et al (7, 8) have previously reported abnormal NE synthesis and urinary output in one patient with OH who had amyloid infiltration of sympathetic ganglia at autopsy. We have demonstrated that peripheral adrenergic fibers are abnormal in amyloidosis and that the intrinsic peripheral vasoconstrictor mechanism remains intact.

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ENVIRONMENTAL NOTES

IRVING J. SELIKOFF, M.D., Editor

Progressive Dyspnea and Diffuse Pulmonary Nodules in a Dentist: A Diagnostic Dilemma*

Submitted by

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Abstract

This study concerns a 35-year old dentist with a productive cough and progressive shortness of breath. Roentgenologic findings indicated interstitial lung disease. The patient's occupation led to suspicion of dust disease (cristobalite exposure). However, no fibrogenic particles were found in mineralogic examination. Careful occupational history revealed an unusual source of this disease—chronic aspiration of petroleum products.

> *When a doctor visits a working-class home he should be content to sit on a three-legged stool, if there isn't a gilded chair, and he should take time for his examination; and to the questions recommended by Hippocrates, he should add one more. What is your occupation?* Bernadino Ramazzini, 1633–1714.

Seldom has simple and practical advice such as Bernadino Ramazzini's had a greater influence on the development of medicine. In one innocent-sounding sentence we find that Ramazzini characterizes and supersedes the medical practice of two thousand years (1).

Societal development and industrial growth offer modern man a great variety of working environments; in these days, an individual will frequently encounter several places of work during his or her lifetime and may, thereby, experience a variety of occupational exposures. This can be the result of the individual's own preference or choice, but is often a result of assignment to certain tasks determined by others.

Over the centuries, it has become necessary to modify Ramazzini's classic question to "what have your occupations been throughout your life?"—that is, a lifetime occupational history. This modification has turned out to be of great

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importance in occupational medicine because many occupational and environmental diseases are commonly the result of exposure so long ago, and for such a short period of time, that they escape the patient's spontaneous recollection.

Although the condition about to be described does not come regularly to the attention of the average occupational physician, the natural history of the disease and the diagnostic approaches utilized may serve as a useful paradigm.

Case Report

The patient is a 35-year-old Taiwanese dentist who, approximately five years prior to the current examination, experienced cough and progressive exertional dyspnea. Since then, the cough has produced a whitish-yellow sputum, occasionally streaked with blood; and the patient noted a weight loss of 20–30 pounds accompanied by anorexia. Chest discomfort was reported, but no actual chest pain. There was no definite history of wheezing. Early history was basically unremarkable; no history of measles, pertussis or episodes of pneumonia, pleurisy or clinical tuberculosis. There had been no unexplained febrile disease in the past. There was no history of any sinus condition or prolonged use of nose drops. The patient never smoked cigarettes. Occupational history did not initially identify any specific industrial exposure. Patient's father is a dentist. The patient began working as a dental assistant at the age of 20, and is currently a practicing dentist.

Physical examination revealed mild respiratory distress at rest, viz., the patient's cough producing yellowish, foamy, viscous sputum. No clubbing or edema was noted. Temperature 98°F; blood pressure 150/90 mm Hg. Lacrimal glands were not enlarged. No lymphadenopathy. Pulmonary auscultation revealed inspiratory and primarily expiratory rhonchi. Examination of the heart was unremarkable.

Extensive laboratory work-up was also unremarkable. A mixed obstructive-restrictive pulmonary pattern with hypoxia at rest was noted, however: VC 41% of predicted, FEV_1/FVC 54%, FEV_3/FVC 82%. MVV 31% of predicted; D_LCO 12.5 ml/min/mm Hg. Arterial blood gases at rest: pH, 7.38; PO_2, 71; PCO_2, 41. The remainder of the studies, including multiple cultures for tuberculosis, fungus, parasites, and sputum cytology were negative, as were serologic studies including ANA, antistreptolysin, C-reactive protein, studies for rheumatoid arthritis, and LE tests. IgM was elevated at 290 mg% (normal 104 mg%). Sweat test was negative. ^{99m}Tc perfusion lung scan and ^{99m}Tc-S colloid aerosol inhalation lung scan were suggestive of chronic obstructive pulmonary disease of bronchitic type. Fiberoptic bronchoscopy was non-diagnostic. A chest roentgenogram showed a fine, nodular interstitial type pattern (Fig. 1).

Because of these findings, the patient was further evaluated by open lung biopsy. Hematoxylin-eosin slides were reviewed at the Environmental Sciences Laboratory. Neither silicotic nodules nor asbestos bodies were observed. However, a striking bronchopneumonia was found with accumulation of large, clear, macrophages filled with lipid substance in the peribronchiolar connective tissue, alveolar spaces, and septum. These lesions were multiple and suggestive of "lipoid pneumonia" (Fig. 2). Histochemical analysis was not done.

Discussion

The roentgenographic findings were consistent with severe, diffuse, interstitial lung disease. Silicosis was the most plausible roentgenologic diagnosis. This diagnosis was also consistent with several other laboratory and clinical findings.

In recent years, increased attention has been focused on potential health hazards associated with the use of dental materials, in addition to mercury, beryllium, and other toxic metals. Dental materials frequently consist of nonmetallic components, such as diatomaceous earth, which can cause pulmonary fibrosis. Microscopic and elemental analyses have indicated that

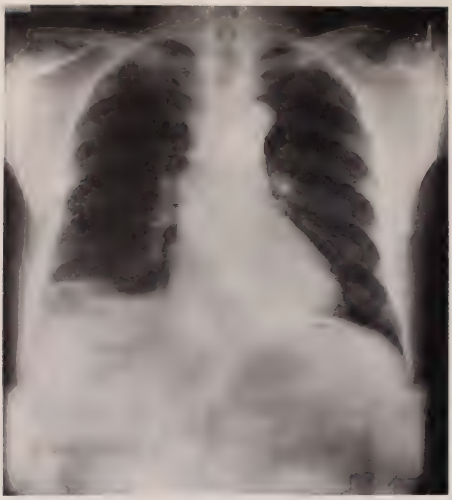

FIG. 1. Chest roentgenogram showing fine nodular interstitial type pattern.

siliceous particles are a major constituent of alginate powder aerosols frequently encountered in dental practice (2). For example, diatomaceous earth is a common constituent of alginate dental impression materials. For industrial use, diatomaceous earth is heated to temperatures sufficiently high thermally to transform the diatom shell from amorphous opal to a crystalline form of silica, cristobalite, which is considerably more fibrogenic than the ordinary form of silica, i.e., quartz. The exposure to silica dust raised the possibility of silicosis. In order to confirm this, histologic sections of the patient's lung tissue were prepared by a carbon extraction technique (3). Systematic scanning of a representative number of electron microscopic preparations showed that very few mineral particles were present in the lung tissue. The result of the open biopsy showing signs of "lipoid" pneumonia, and the absence of inorganic particles in lung tissue on mineralogic analysis made a diagnosis of pneumoconiosis unlikely. In addition, the absence of other occupational exposure to silica dust and the patient's young age further strengthened the case against silicosis.

Lipoid pneumonia, suggested by the histopathologic examination in this case, is the designation of exogenous disease caused by aspiration of various oils into the lungs and should be distinguished from cholesterol pneumonitis, which is a term used for a pulmonary condition characterized by chronic inflammatory changes and excessive deposits of cholesterol in the tissues.

Although the oils may be both of vegetable and animal origin, mineral oil seems to be the most commonly involved agent. As might be expected, the very young and very old are most frequently affected by aspiration pneumonia.

In contrast to the acute events that are associated with acute aspiration "pneumonia" (Mendelson's syndrome), a more chronic type of aspiration occurs in various conditions of chronic aspiration pneumonia (including Zenker's diverticulum, esophageal stenosis, and neuromuscular impairment of swallowing). In the latter case, the patient is commonly unaware of the aspiration, and the disease process may not warrant the patient's seeking medical attention.

The pathologic characteristics of lipoid pneumonia consist initially of a hemorrhagic bronchopneumonia, especially if animal fatty acids are the etiologic agent. Mineral oil, however, may cause a more chronic insidious reaction in the lungs. In the later stages, the normal lung architecture is replaced by pools of oil surrounded by giant cell foreign body reactions (5). The roentgenologic manifestations of this disease are typically in the form of alveolar consolidation. The oil, however, may be taken from the alveolar spaces by macrophages into the interstitial space so that a predominantly interstitial pattern may develop. The most common form shows relatively homogenous consolidation of one or more segments, and, as might be expected, affects the lower lobes because of gravity. If a large amount of oil has been aspirated over a long period of time, diffuse pulmonary fibrosis and eventually cor pulmonale may develop (6). Because of this variable clinical course, the diagnosis most

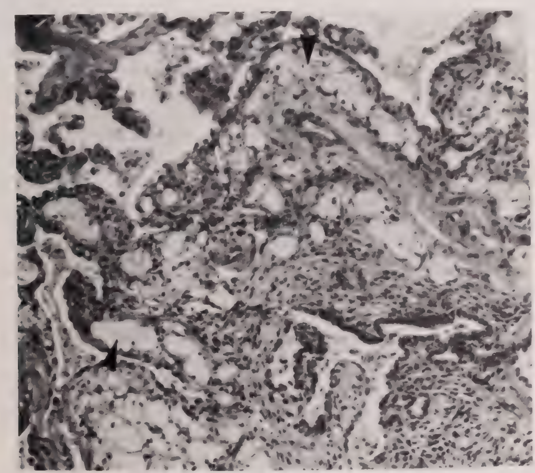

FIG. 2. Photomicrograph showing part of the lung parenchyma with marked thickening of the peribronchiolar connective tissue, in which a large number of lipid containing foam cells (arrows) are seen. (Hematoxylin and Eosin stain 176×.)

frequently is made by pathologists through histologic examination of tissue removed at thoracotomy performed on the basis of a suspect lesion (7, 8); occasionally, the differential diagnoses are "viral pneumonia" or tuberculosis (9, 10).

Finally, this disease should also be distinguished from iatrogenic pulmonary embolism, which is almost invariably a complication of lymphangiography with ethiodized oil (Ethiodol). This condition also may manifest itself roentgenographically as a fine reticular pattern that usually disappears within two weeks. Few of the patients have symptoms (11).

In industrial settings, the low volatility of several aliphatic compounds (kerosene, lubricating oils) usually protects against respiratory tract damage after inhalation. The most common route of entry by which these compounds may cause pulmonary damage is ingestion followed by spontaneous or induced vomiting resulting in aspiration. It has been shown experimentally that ingestion of these compounds alone may not be harmful in the absence of vomiting (12). When this occurs, however, aspiration into the lungs, especially of compounds with low viscosity such as gasoline (13), may follow and lead to an acute event of asphyxia, cardiac arrest, or respiratory paralysis. In addition, there may be central nervous system symptoms following systemic absorption. Aspiration of compounds of higher viscosity, such as motor oil or mineral oil are less readily aspirated and may, therefore, be associated with a slow, progressive disease development—the ultimate result being lipoid pneumonia as described above.

The fact remains that the patient reported here had histopathologic evidence of lipoid pneumonia, and this disease was of exogenous origin. The patient's occupation as a dentist did not provide a plausible source of exposure. Thus, the question arose whether there might have been any other exposure hidden in an incomplete occupational history.

While considering and reconsidering the modified version of Ramazzini's question, additional information revealed that the patient had spent two years (1961–1962) in charge of a motor vehicle maintenance department during his military service; and that almost daily he had transferred gasoline, and possibly other aliphatic hydrocarbons, from barrels to other vessels by inserting a tube into the barrel and applying a negative pressure in the tube with mouth suction, thereby enabling the liquid to flow. Chronic aspiration of these compounds may have followed.

The ensuing disease was a severe diffuse "lipoid pneumonia" for which the therapeutic possibilities, unfortunately, are limited. Although oral cortisone therapy has had some beneficial effect, the prognosis is guarded.

As is often the case, adequate occupational hygiene could have prevented this disease, and strict adherence to the modified version of Ramazzini's suggestion that any work place throughout the lifetime can cause illness both would have facilitated diagnosis and advanced therapeutic intervention.

Acknowledgment

Our gratitude to Dr. Joel Duberstein, Consulting Physician, Morristown Memorial Hospital, Morristown, New Jersey, for referring the patient to us and to Mrs. Reba Nosoff, assistant to the President and Dean of the Medical Center, for her assistance.

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Unusual Problems in Surgery

A. ROBERT BECK, M.D., EDITOR

Diaphragmatic Hernia of Morgagni

Submitted by

MARK A. REINER, M.D., MICHAEL A. BLEICHER, M.D., AND A. ROBERT BECK, M.D.

In 1761, Morgagni (1) first described the uncommon anterior diaphragmatic hernia that now bears his name (2–6). Other names for this entity are parasternal, retrocostoxiphoid, retrosternal, and subcostosternal hernia. Two cases are presented. A simple, safe transabdominal repair of foramen of Morgagni hernia is described based upon the experience of the second case.

Case Reports

Case 1: B.B.—EGH #428551. A 1500-gram male infant was delivered by low forceps to an 18-year-old gravida II, para I, abortion 0 black female after 36 weeks gestation. There was no evidence of neonatal distress. Physical examination at birth was unremarkable except for an anterior bulging of the right lower ribs (Fig. 1), bilateral inguinal herniae and bilateral cryptorchidism. Auscultation of the chest revealed normal heart and breath sounds bilaterally. Chest x-rays demonstrated a 3 × 4 cm density located anteriorly and to the right of the heart (Figs. 2A, 2B). A diagnosis of hernia of Morgagni was made and later substantiated when a radioactive gold^{198} scan documented the presence of a portion of the right lobe of the liver in a right supradiaphragmatic position (Fig. 3).

The child initially did well. Intermittent cyanosis and dyspnea during feedings occurred at age 18 days. Examination revealed a dusky infant with a pulse of 160 beats per minute, a respiratory rate of 40 per minute, and for the first time a grade II/VI systolic murmur. The patient improved after administration of intravenous fluids, antibiotics, and oxygen.

At 26 days of age the infant suffered a second episode of acute respiratory difficulty with tachycardia, tachypnea and supra- and substernal retractions. Crepitant rales were heard at both lung bases and the systolic murmur increased in intensity. Digoxin therapy was initiated, but the child continued to deteriorate and had multiple cardiopulmonary arrests until his demise at age 30 days. Postmortem examination showed an enlarged heart with all four chambers dilated, a widely patent foramen ovale and a high ventricular septal defect. The lungs had areas of patchy atelectasis with evidence of pulmonary edema. The right lower anterior chest showed an outward bulging deformity. The right hemidiaphragm had an anteromedial defect covered only with peritoneum. A portion of the liver was protruding into the anterior mediastinum and right hemithorax through this defect, causing mild compression of the right lung and shifting the heart to the left (Fig. 4). The cause of death was cardiac failure and pulmonary edema secondary to the ventricular septal defect. The hernia of Morgagni did not contribute to the death of the child.

Case 2: AB, EGH #905686. This infant, the third child of a 27-year-old black woman, was the product of a full-term, uncomplicated pregnancy delivered by Cesarean section performed for fetopelvic disproportion. Birth weight was 3300 grams.

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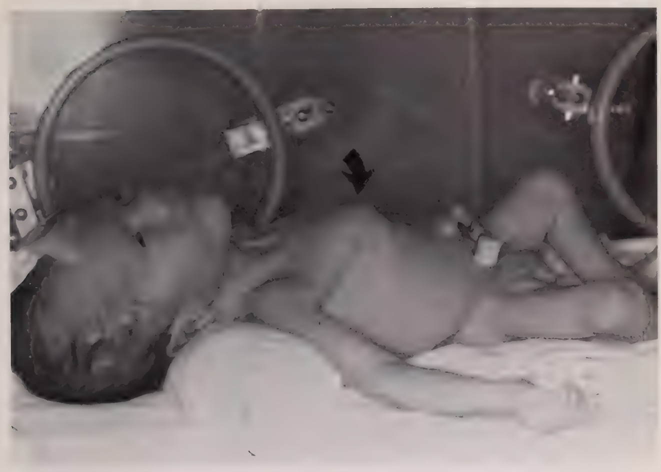

FIG. 1. Case 1. Note anterior bulging of the right lower thorax.

The child thrived until 14 weeks of age when he developed a productive cough followed by nonbilious vomiting. He was brought to the Emergency Department with a temperature of 100.2°F, a heart rate of 160 beats per minute and a respiratory rate of 30 per minute. The patient's weight was 4750 grams and physical examination revealed coryza, pharyngitis and wheezes. No cardiac murmur or apparent congenital abnormality was present. Laboratory data revealed a Hemoglobin of 12.5gm%, white blood cell count of 8000 cells per mm^3 with a normal differential, normal urinalysis, and normal blood chemistry. Chest x-rays demonstrated clear lung fields. However, there was a right paracardial mass in the anterior mediastinum in continuity with the diaphragm. It appeared solid and without gas pattern (Figs. 5A, 5B). A diagnosis of Morgagni hernia was made and later supported when a Technetium scan documented extension of the left liver lobe to the substernal and medial aspect of the right hemithorax (Fig. 6).

Ten days after admission, bronchiolitis resolved and the child underwent laparotomy through a right subcostal incision. An anterior, 2 × 3-cm, retrosternal hernial defect with extension to the right was found. The hernial sac did not contain muscle fibers. An accessory left liver lobe comprised the actual mass visualized on chest x-ray. Primary closure of the defect, after reduction of the liver, was accomplished by plicating right and left hemidiaphragmatic leaves with 2-0 silk sutures placed interruptedly. The sac was not opened, but reduced and incorporated within the repair. This maneuver obliterated the dead space without entry into the chest cavity. The plication was easily performed because there were no adhesions of the hernial sac to pericardium or to lung parenchyma.

Postoperative chest x-ray (Fig. 7) revealed a normal right hemidiaphragmatic contour, without evidence of pneumothorax or pneumopericardium. The child's recovery was uneventful and he was discharged from the hospital on the seventh postoperative day.

Discussion

The etiology and actual anatomic site of the Morgagni hernial defect are unclear (7, 8). Embryologically, the diaphragm is derived from three main components: the septum transversum, the pleuroperitoneal membrane with its

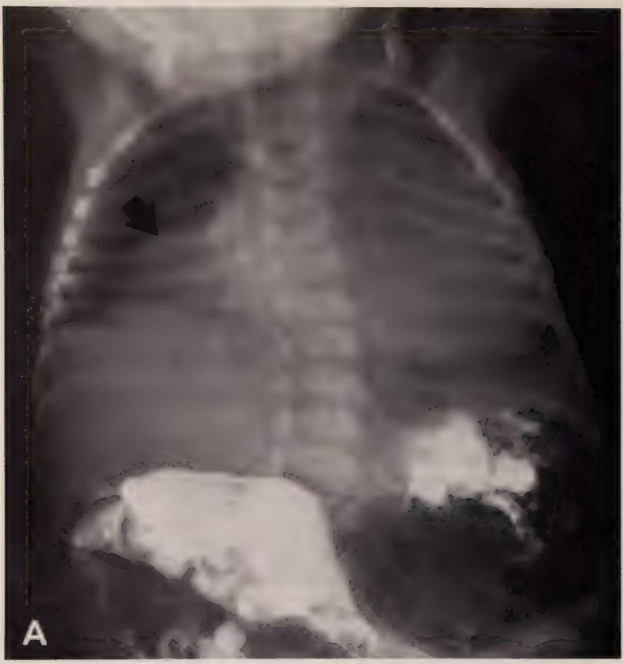

FIG. 2A. Case 1. Chest x-ray demonstrates a right anterior paracardial mass.

support from the lateral and dorsal body walls, and the dorsal or esophageal mesentery (9). The central tendon is derived from the septum transversum, a thick mesodermal plate originally occupying the space between the pericardial cavity and the stalk of the yolk sac. This forms beneath the heart at the eighth week of fetal life and migrates dorsally until it fuses with the mesentery of the foregut. This mesentery ultimately becomes the diaphragmatic crura.

The only remaining defects are posterior and lateral. The pleuroperitoneal folds or membranes then fill the defects, obliterating the connection between the thoracic and abdominal portions of the coelomic cavity. A postero-lateral fold of mesenchyme from the lateral and dorsal bodies adds support and creates the plane for myoblastic migration into the pleuroperitoneal membranes. These muscle-forming cells are derived from the third through fifth cervical segments giving the diaphragm its phrenic nerve innervation. The left side fuses later than the right, and the posterior segments close last. Failure in fusion, or failure of muscularization of the pleuroperitoneal membrane gives

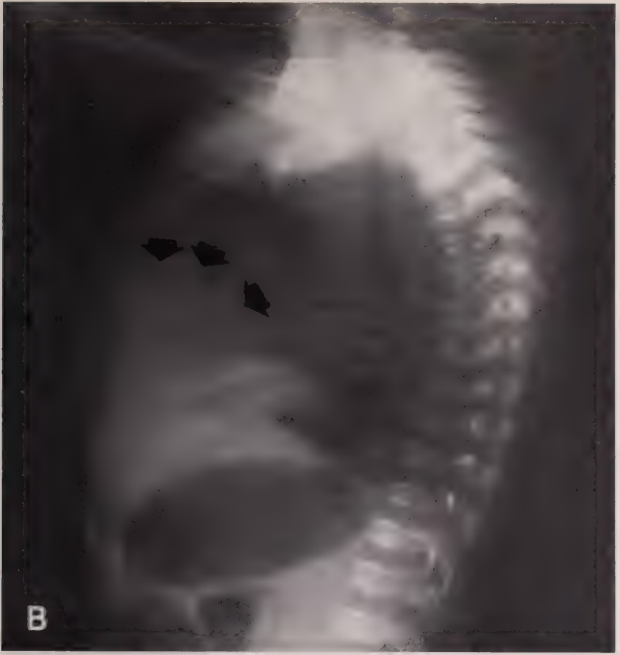

FIG. 2B. Case 1. Lateral chest x-ray.

rise to a Bochdalek hernia. Developmental failure anteriorly, in the retrosternal segment of the septum transversum may result in a hernia of Morgagni. The exact etiology of this defect remains obscure. The true diaphragm interdigitates with the transversus abdominus muscle anteriorly and any failure to adequately fuse may leave a potential defect for herniation. The superficial epigastric artery runs through the foramen of Morgagni, a potential space not in the diaphragm but rather in the fibers of the transversus abdominis and posterior lamina of the rectus sheath (7).

This space may enlarge with increased intraabdominal pressure, ultimately permitting herniation to occur. Failure of myoblastic proliferation within the septum transversum or failure of fusion between the anterior ribs, costal cartilage and sternum (4) may be other causes for the hernial defect. A Morgagni hernia occurs more frequently on the right side and this may be explained by the added support to the left hemidiaphragm by the heart and pericardium (3).

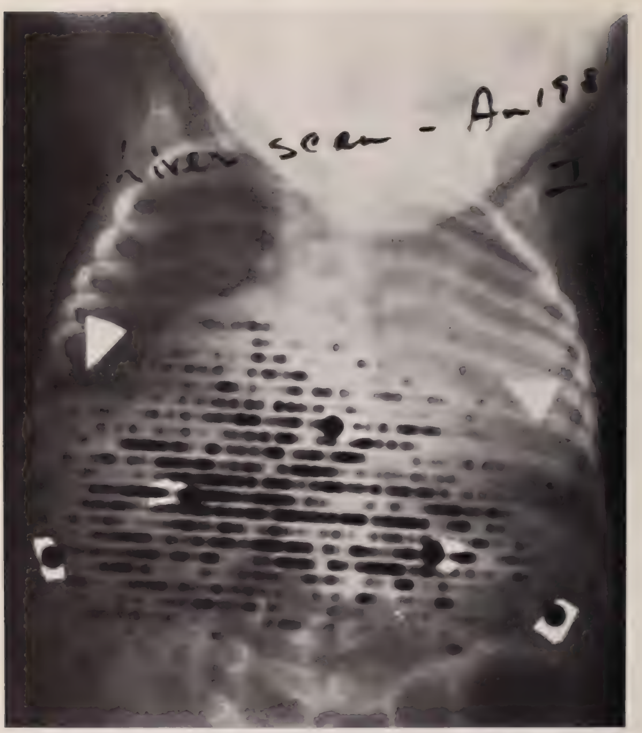

FIG. 3. Case 1. Radioactive gold scan superimposed on chest x-ray documents presence of liver within hernia.

Symptoms are variable and depend upon the age of the patient and the contents of the hernial sac. Severe respiratory compromise secondary to direct compression of the lung (2), recurrent respiratory tract infections or symptoms related to entrapped bowel are uncommon in infants and children. The majority of patients are asymptomatic and the hernia is discovered on chest x-ray. The hernial sac may contain liver, spleen, stomach, omentum or large or small bowel. Recurrent intestinal obstruction and occasional viscous infarction are more common in the adult, but also have been reported in infants and children (2).

When evaluating a neonate with cyanosis and a Morgagni hernia, cardiac disease and not the hernia must be considered as the probable cause of

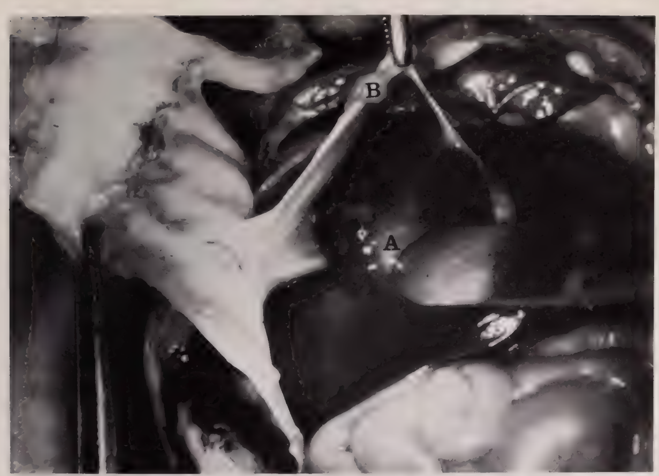

FIG. 4. Case 1. Postmortem examination showing a portion of the right lobe of liver (A) within a thin walled hernial sac (B).

pulmonary compromise. Our first case illustrates this point. Greenwood (12) reports an incidence of 23% cardiac abnormalities with congenital diaphragmatic herniae.

Physical findings in patients with Morgagni hernia are sparse. Occasionally bowel sounds may be heard in the chest. Our first case had a deformity of the thoracic cage over the hernial site. Bingham (13) previously reported this association in two cases. In the absence of physical findings, suspicion is aroused by the presence of a paracardial mass on chest x-ray, which may appear solid or air-filled. The differential diagnosis should include hemangioma, lipoma, lymphoma, pericardial or pleural cyst, teratoma or thymoma. A lateral chest x-ray will reveal an anterior lesion and often demonstrate the "sign of the cane" (14). This is a radiographic finding demonstrating a parietal-properitoneal-peritoneal line that is present substernally and looks like the profile of a cane handle (14). If there is a solid mass at the cardiodiaphragmatic border, a Technetium scan of the liver should always be performed to determine if a portion of liver lies in a supradiaphragmatic position. If there is air within the lesion, then contrast studies of the stomach, small and large bowel should be performed. A solid mass with a normal liver scan can consist of omentum, which can be documented by the technique of induced pneumoperitoneum. This procedure is not without hazard and its use should be judiciously applied.

Controversy over indications for surgical repair exists. Acute pulmonary or

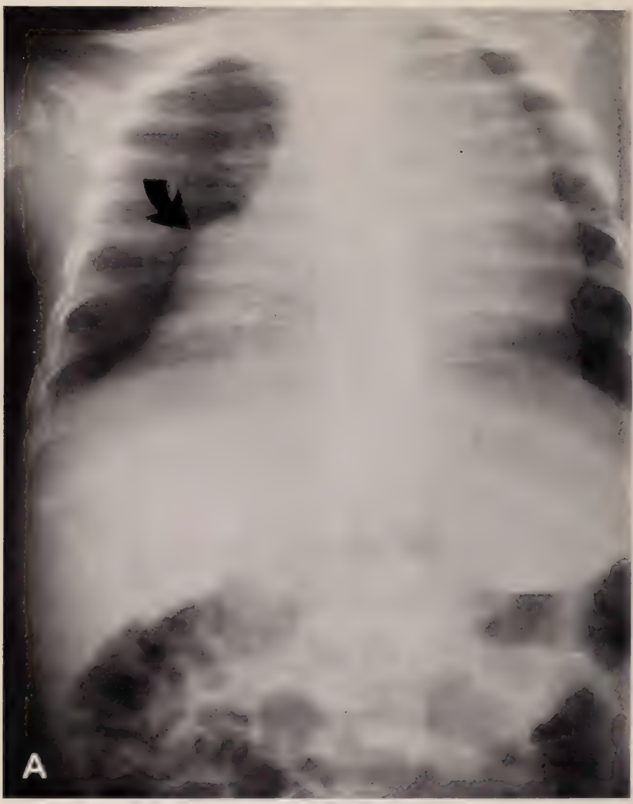

FIG. 5A. Case 2. Chest x-rays showing a right anterior mediastinal mass.

gastrointestinal compromise requires emergent repair. Chin (15) and Wollock (11) advocate no surgery for the asymptomatic condition in adults. Baron (3), Thomas (2), Bentley (10) and Ketonen (16) recommend prompt surgical correction in all patients, adults or children. These authors are supported by the reported cases of incarceration and strangulation of bowel in all age groups (2, 3, 10, 16).

The diaphragmatic hernia may be approached through the abdominal or thoracic cavity. Chin (15) favors the thoracic incision because of the ease in identifying and mobilizing the sac if pleural or pericardial adhesions exist. This

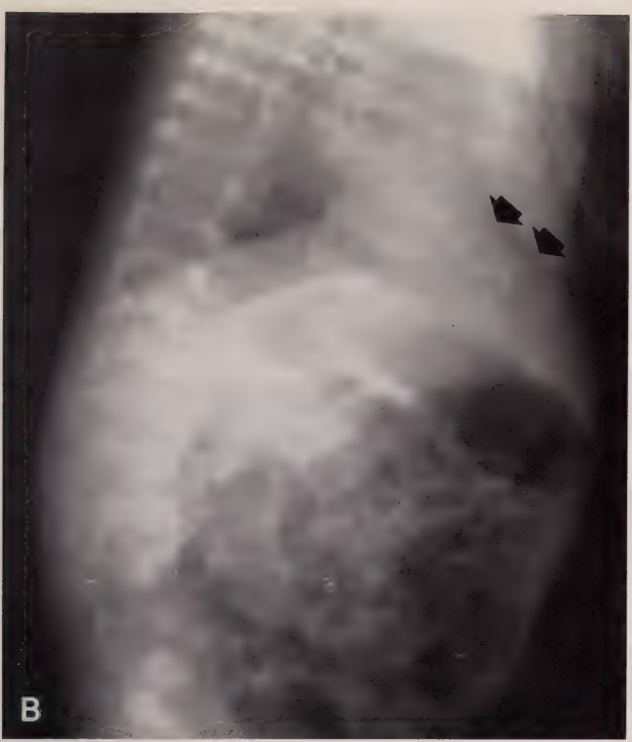

FIG. 5B. Case 2. Lateral chest x-ray.

is the preferred approach if the diagnosis is uncertain. In documented cases of Morgagni hernia, the majority of surgeons favor an abdominal incision (2, 3, 10, 11). Each hemidiaphragm can be visualized and repaired if a bilateral defect exists. Abdominal contents can be easily reduced and a bowel resection performed if indicated. Occasionally, complete reduction of the hernial contents into the peritoneal cavity will not be possible and a ventral hernia or silastic sac will have to be created (17). This can only be done through a transabdominal approach.

Abdominal repair has been performed either by leaving the sac intact or by puncturing the apex of the sac, reducing the hernial contents and imbricating the defect. The former method leaves a defect that may fill with fluid and may act as a potential source of infection. The latter method causes direct entry

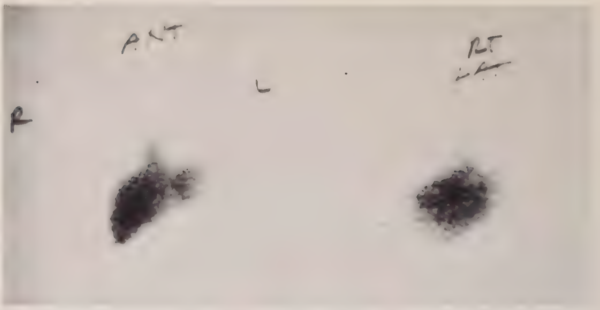

FIG. 6. Case 2. Technetium scan reveals the presence of a portion of the left lobe of liver in the right hemithorax.

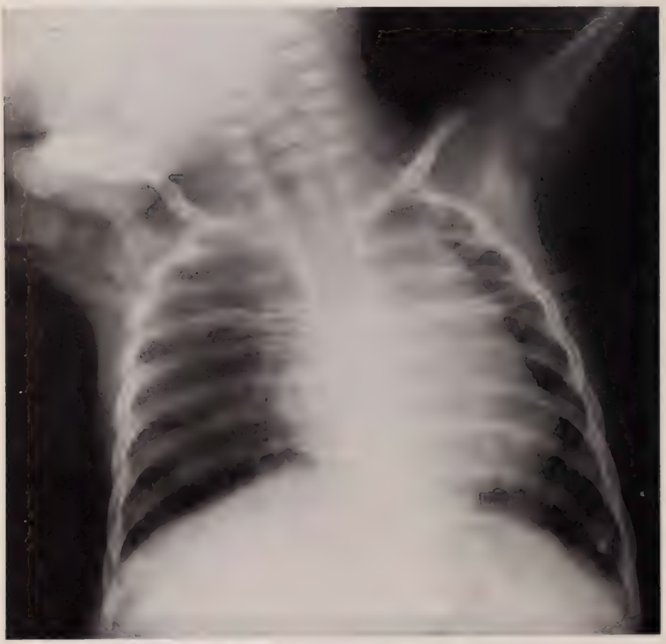

FIG. 7. Case 2. Postoperative chest x-ray.

into the pleural cavity with the possibility of producing a pneumothorax or pneumopericardium (2).

A simple, yet previously undescribed, approach was employed in our second case. A transabdominal repair was accomplished by reducing the herniated portion of liver and incorporating the hernial sac directly within the sutures used to obliterate the diaphragmatic defect. This method eliminates dead space while still obviating entry into the pleural cavity. The technique is applicable to children because of the lack of adhesions between the hernial sac and the surrounding thoracic structures.

Summary

Two cases of diaphragmatic Morgagni hernia in infants are presented. This type of hernia may manifest either as an acute pulmonary or gastrointestinal problem in the neonate or as a chronic one in older children and adults.

In a neonate with delayed onset of respiratory distress, cardiac disease must be excluded before concluding that pulmonary compromise is due to the hernia. The only physical clue to this disease entity is the rare occurrence of anterior thoracic cage bulge. Any patient with a paracardial, anteromediastinal, or cardiodiaphragmatic solid lesion on chest x-ray requires a liver scan to rule out a retrosternal herniation of the liver.

Once the diagnosis is established, transabdominal repair should be performed to avoid possible complications of the anomaly. Infants undergoing repair should have simple reduction of the hernia with incorporation of sac into diaphragmatic sutures to avoid dead space, pneumothorax or pneumopericardium.

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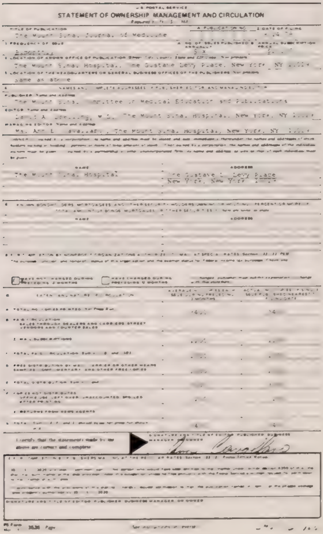

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